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Review Article

Male Reproductive Hazards Associated with Cadmium Exposure

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Abstract: Cadmium, an environmental pollutant prevalent in various industrial surroundings, poses a substantial risk to male fertility. This review explores the complex mechanisms through which cadmium exerts its toxic effects on the testis. The testis, a primary target for cadmium accumulation, experiences structural and functional alterations that disrupt essential cellular processes associated with spermatogenesis. Cadmium-induced testicular injury involves a cascade of events, including apoptosis, autophagy, oxidative stress, inflammation, and disruptions in key signaling pathways. These molecular and cellular changes collectively contribute to compromised testicular function, leading to impaired sperm development and functional activity. Understanding these mechanisms is crucial for delineating the comprehensive impact of cadmium on male fertility. Furthermore, such information opens avenues for developing targeted interventions aimed at mitigating the adverse effects of cadmium exposure on male reproductive function. This review aims to consolidate current research findings, providing a comprehensive overview of the intricate mechanisms underlying cadmium-induced testicular injury and its implications for male fertility.

Keywords: Cadmium; Autophagy, Apoptosis; Spermatogenesis; Testis.

1. INTRODUCTION

Environmental pollutants can contribute to a range of health issues, particularly infertility [1]. Cadmium, a highly toxic metal without a clearly defined biological role, presents a significant public health concern, particularly in terms of reproductive toxicity [2, 3]. Numerous studies have highlighted the heightened sensitivity of human testes to cadmium, leading to toxicity in male reproductive organs, especially the testicles and sperm parameters, owing to the active cell division and metabolism in these tissues [4-10]. Before fertilization can occur, sperm must navigate through several challenges during activation to attain fertilization competence [6]. These biological processes are often triggered by the activation of ion channels on the sperm membrane [10]. Sperm possesses a unique cation channel known as CatSper, acting as the primary source of intracellular Ca2+, inducing various Ca2+-dependent responses such as sperm motility/viability, progesterone-induced acrosome reaction, and chemotaxis. Additionally, the sperm-specific potassium channel (KSper) is responsible for membrane potential hyperpolarization. Both CatSper and KSper play crucial roles in regulating sperm physiology and, consequently, male fertility [11]. Cadmium is believed to disrupt protein tyrosine phosphorylation by competing for the

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binding of calmodulin with calcium [12]. Furthermore, cadmium has been observed to impede axonal protein phosphorylation by increasing membrane lipid peroxidation. The deleterious impact of cadmium on sperm metabolism is evident through the inhibition of glycogen phosphorylase, magnesium-dependent ATPase, glucose-6-phosphatase, and succinate dehydrogenase [13]. Elevated cadmium concentrations contribute to male infertility by impairing the functional activity of these channels, resulting in altered expression, permeability, and decreased blood pH, ultimately leading to reduced sperm viability and motility [11].

Cadmium, a heavy metal ubiquitous in the environment due to industrial activities and pollution [14-16], poses a significant threat to male reproductive health. Extensive research has demonstrated the adverse effects of cadmium exposure on the male reproductive system, particularly on the testes [17, 18]. The testes, responsible for spermatogenesis and androgen hormone production, are highly susceptible to cadmium-induced damage [19]. Cadmium enters the body through various routes, including ingestion, inhalation, and skin absorption, accumulating over time due to its persistent nature [20-22]. Once accumulated, cadmium disrupts crucial cellular processes in the testes, leading to impaired spermatogenesis and hormonal imbalance [23]. The intricate regulatory mechanisms of the steroidogenic pathway, essential for male reproductive function, are particularly vulnerable to cadmium toxicity. Studies have indicated that cadmium disrupts the expression of key proteins involved in spermatogenesis, such as STAR, P45011A1, P45017A1, 3β-HSD, 17β-HSD, Scarb1, and Lhcgr, leading to testicular dysfunction [24]. Furthermore, cadmium-induced alterations in Nano-scale exosome secretion by Leydig cells, along with disruptions in autophagy and apoptosis pathways, contribute to the overall testicular injury [25].

The main role of the testes is to produce sperm storage, they're also vital for producing testosterone and other male hormones known as androgens [26-28]. The testes, where sperm development takes place, are susceptible to cadmium accumulation, disrupting the delicate balance of cellular and molecular processes [29, 30]. Cadmium interferes with the intricate hormonal regulation essential for spermatogenesis, impacting Leydig cells responsible for testosterone production and Sertoli cells crucial for nurturing developing sperm [31]. Cadmium-induced oxidative stress and DNA damage further contribute to the impairment of sperm development [32]. Cadmium disrupts the normal functioning of germ cells, leading to abnormal sperm morphology, reduced sperm motility, and increased sperm abnormalities [33]. These alterations not only compromise male reproductive potential but also pose a risk to overall reproductive health. In addition, cadmium also disrupts the different homeostasis pathways of testicular cells.

Apoptosis plays a pivotal role in maintaining tissue homeostasis, eliminating damaged cells, and regulating cell populations. However, dysregulation of apoptosis, especially its induction in healthy cells, can lead to tissue damage and dysfunction [34]. Cadmium's ability to trigger apoptotic pathways in the testis raises concerns about its impact on male reproductive health. Cadmium-induced testicular damage is characterized by an upregulation of caspase 3 and 9 expression, contributing to morphological evidence of apoptosis. This includes chromatin decondensation and marginalization in primary spermatocytes, loss of the nuclear envelope in spermatogonia, alterations in DNA distribution, degradation of cytoplasmic organelles, and disruption of mitochondrial membrane potential [35]. Apoptosis induced by cadmium has been observed in the testes of various mammalian species [36-38]. In humans, the concentration-dependent impact of cadmium on the death of embryonic germ cells has been demonstrated through the detection of caspase 3 enzyme activity in testicular tissue [39]. The caspase 8, caspase-3-p53 pathway may interact with cadmium-induced intrinsic and extrinsic apoptotic mechanisms in reptiles [40, 41].

Autophagy is triggered in response to cellular stress, and cadmium exposure has been linked to the activation of autophagic pathways in testicular tissues [28, 42]. This phenomenon is evidenced by the presence of increased levels of autophagic markers, such as LC3 and Beclin-1, indicating the initiation of autophagosome formation [43]. Autophagy emerges as a crucial cellular response to this toxic insult. Autophagy is a conserved catabolic process involved in the degradation and recycling of cellular components, maintaining cellular homeostasis and responding to various stressors [20]. Autophagy serves as a double-edged sword – it can act as a cytoprotective mechanism by removing damaged cellular components, or it may contribute to cell death under prolonged or severe stress conditions. Cadmium ability to disrupt cellular redox balance, induce oxidative stress, and interfere with signaling pathways contributes to the initiation of autophagic processes in testicular cells [42]. These consequents suggest that cadmium-induced alterations in the testicular milieu encompass oxidative stress, inflammation, and interference with essential signaling pathways, collectively contributing to compromised sperm development (Figure 1). The testis, being a primary target for cadmium accumulation, experiences structural and functional changes that directly impact the sperm's reproductive competence.

2. CADMIUM EXPOSURE ON SEMEN PARAMETERS

Cadmium (Cd) exposure has garnered significant attention in recent years due to its detrimental effects on human health, particularly in the context of reproductive health. Cd, is a toxic heavy metal, found in various sources such as industrial emissions, tobacco smoke, and contaminated food and water. Its widespread presence poses a significant risk to human populations,

with numerous studies highlighting its adverse impact on various physiological systems. A particular concern is the association between Cd exposure and semen parameters in males. Semen quality, a critical determinant of male fertility, is influenced by multiple factors, including environmental exposures. Emerging research has elucidated a negative correlation between Cd exposure and semen parameters, encompassing sperm density, motility, morphology, and concentration. This correlation underscores the potential reproductive hazards posed by Cd contamination and emphasizes the importance of understanding its effects on male reproductive health [36].

Numerous epidemiological studies and experimental research have provided compelling evidence linking Cd exposure to adverse effects on semen quality. These studies have revealed consistent patterns of decreased sperm density, impaired motility, abnormal morphology, and reduced sperm concentration in individuals exposed to elevated levels of Cd. Furthermore, the deleterious effects of Cd on semen parameters have been observed across diverse populations and geographical regions, highlighting the universal nature of this association [38].

The mechanisms underlying Cd-induced alterations in semen parameters are multifaceted and complex. Cd exerts its toxic effects through various pathways, including oxidative stress, disruption of hormonal regulation, and interference with spermatogenesis. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms, is a primary mechanism implicated in Cd-induced sperm damage. Additionally, Cd can disrupt endocrine function by interfering with hormone synthesis, secretion, and receptor binding, thereby compromising spermatogenesis and sperm quality [30].

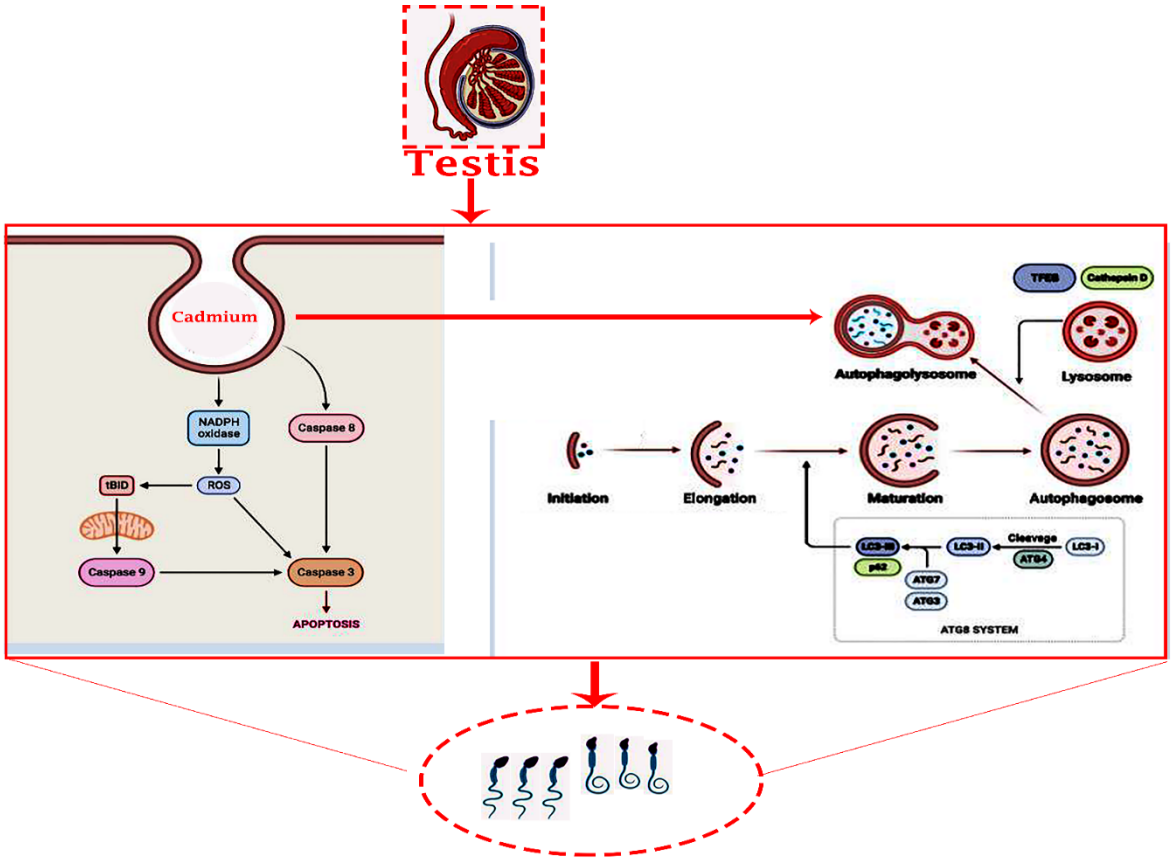

Fig. 1: Structural and functional changes in testes

3. MATERIALS AND METHODS

This review article synthesizes existing literature and research findings to comprehensively elucidate the mechanisms underlying cadmium-induced testicular injury and its impact on male fertility. The methodology employed for this review is as follows:

Extensive searches were conducted across various scientific databases including PubMed, Google Scholar, Scopus, and Web of Science. Keywords such as "cadmium," "testis," "male fertility," "spermatogenesis," "apoptosis," "autophagy," "oxidative stress," "inflammation," and "signaling pathways" were used alone and in combination to identify relevant articles.

Studies published in peer-reviewed journals, as well as review articles, meta-analyses, and systematic reviews, were included in the review.

Articles were screened based on relevance to the topic of cadmium toxicity and its effects on the male reproductive system. Preference was given to studies that investigated the molecular and cellular mechanisms underlying cadmium-induced testicular injury. Both in vivo and in vitro studies, conducted in various experimental models including rodents, humans, and cell cultures, were considered for inclusion. Data from selected studies were extracted, including experimental design, methods, results, and conclusions. The extracted data were synthesized to identify common themes and patterns related to the toxic effects of cadmium on the testis. The collected data were critically analyzed to evaluate the strength of evidence supporting the identified mechanisms of cadmium-induced testicular injury. Key findings were interpreted in the context of existing knowledge and theories in the field of reproductive toxicology and environmental health.

The synthesized data were organized thematically to provide a comprehensive overview of the mechanisms through which cadmium exerts its toxic effects on the testis. Emphasis was placed on elucidating the interplay between apoptosis, autophagy, oxidative stress, inflammation, and disruptions in signalling pathways in the context of cadmium-induced testicular injury.

Through the meticulous synthesis and analysis of available literature, this review aims to provide a comprehensive understanding of the intricate mechanisms underlying cadmium-induced testicular injury and its implications for male fertility.

4. CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, the mechanisms of cadmium-induced testicular injury pose a significant risk to male fertility, necessitating a comprehensive understanding of the intricate pathways involved. Cadmium, a pervasive environmental pollutant, targets the testis, leading to structural and functional alterations that compromise crucial processes associated with spermatogenesis. Oxidative stress emerges as a central player in cadmium-induced testicular injury, triggering a cascade of events, including inflammation, apoptosis, and autophagy. These processes collectively contribute to the disruption of testicular function, resulting in diminished sperm quantity and quality. The intricate interplay of various molecular pathways underscores the complexity of cadmium's impact on male reproductive health. Future research should focus on elucidating the specific molecular targets within these pathways, allowing for the development of therapeutics aimed at ameliorating cadmium-induced testicular injury. Additionally, regulatory measures to minimize cadmium exposure in occupational and environmental settings are crucial for preventing reproductive health hazards. The negative correlation between Cd exposure and semen parameters, encompassing sperm density, motility, morphology, and concentration, underscores the urgent need for comprehensive strategies to mitigate Cd contamination and protect human fertility. Addressing this issue requires interdisciplinary efforts, including rigorous regulatory measures, public health interventions, and further research to elucidate the underlying mechanisms and develop targeted interventions to safeguard male reproductive function in the face of Cd exposure.

Overall, a multidisciplinary approach is imperative to unravel the complexities of cadmium-induced testicular injury and devise effective strategies to safeguard male fertility.

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