



Mechanisms of Cadmium-Induced Testicular Damage

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Abstract

Testicular damage is one of the deleterious effects of cadmium (Cd) toxicity. Cadmium is a serious contaminant to the environment that causes severe damage to a variety of tissues and organs including the liver, kidney, and testes. Moreover, cadmium compounds are classified as carcinogenic substances in humans. Acute and chronic cadmium intoxication results in the formation of reactive oxygen species (ROS), attenuation of anti-oxidant enzyme activity and inducing oxidative stress. In addition, inflammation is induced by cadmium toxicity. So, both oxidative stress and inflammation play an important role in the pathogenesis of testicular damage under cadmium exposure. Oxidative stress is triggered by reactive oxygen species (ROS) and an imbalance between ROS and antioxidant enzymes activities. Oxidative stress activates the NF- κ B signaling pathway, which controls several genes implicated in inflammatory responses such as TNF- α and iNOS. Cd can pass through the blood-testes barrier, causing changes in the hypothalamic-pituitary-testicular axis and DNA damage. The harmful effect of cadmium on testes is known to be germ cell degeneration and impairment of testicular steroidogenesis due to damage in testicular Leydig cells.

Keywords: Testicular damage, cadmium, oxidative stress, inflammation.

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1. Introduction

Chemical exposure is the most common cause of infertility in the world (Jurewicz et al. 2014). These environmental toxic contaminants include heavy metals as cadmium, lead, and mercury (Benoff et al. 2000, Sukhn et al. 2018). Cadmium toxicity may result from occupational exposure because of working with cadmium-containing pigments, plastics, glass, metallic alloys, and electrode material in batteries or non-occupational exposure which results from smoking, air pollution, and consumption of cadmium-contaminated water and sea foods (Waisberg et al. 2003). Based on the variety of target organs of cadmium-induced toxicity, many in vitro studies investigated the carcinogenic effect of cadmium on different cell

types and the obtained data directed the International Agency for Research on Cancer to categorize cadmium as a group I human carcinogen (Medina et al. 2017, Thévenod & Lee 2013). Unlike most heavy metals, cadmium induces harmful effects at relatively low doses once absorbed by the body (Ciarrocca et al. 2013).

1.1. Molecular and cellular mechanisms of cadmium toxicity

Cadmium-induced cellular injury is caused by different mechanisms (Angenard et al. 2009, Niknafs et al. 2015, Oliveira et al. 2012). Firstly, cadmium-calcium interactions, in which cadmium may enter cells through calcium channels and compete with calcium to bind calmodulin that interferes with calmodulin-dependent physiological

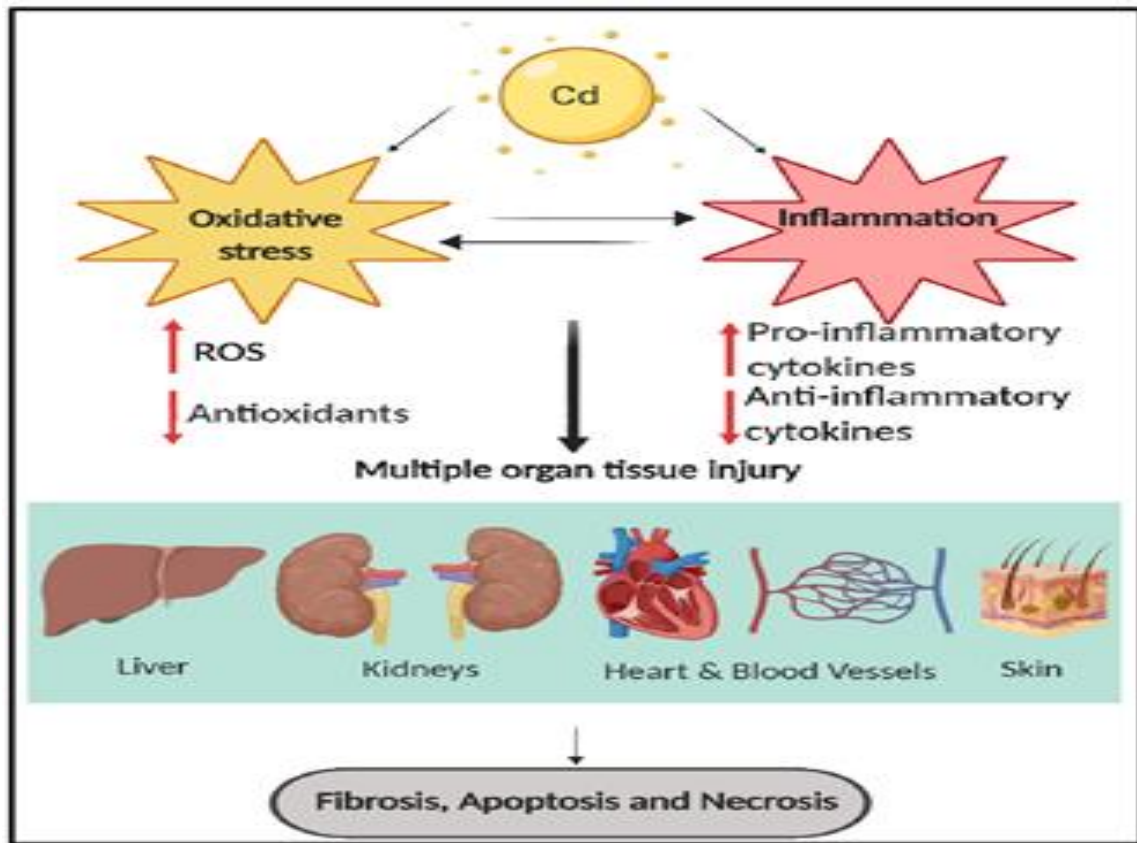


Figure 1. The impact of cadmium toxicity leading to multi-organ tissue injury (Das et al. 2019).

and biochemical processes (Akinloye et al. 2006, Vandenberg et al. 2012). Then, cadmium may interact with the hydroxyl, mercapto, and amino groups of proteins to generate cadmium-protein complexes, which can suppress or inactivate multiple enzyme systems, which can have a harmful effect on biological activities (Luevano & Damodaran 2014).

Cadmium can affect the expression of apoptotic genes (Niknafs et al. 2015, Veeriah et al. 2014), induce abnormal gene expression and inhibit DNA damage repair. Cadmium exposure increases the mRNA expression level of the pro-apoptotic Bax gene and decreases the mRNA expression level of the anti-apoptotic Bcl-2 gene. Thereby, it increases the Bax/Bcl-2 ratio and induces apoptosis of cells (Alian et al. 2018, Breton et al. 2013).

1.2. Cadmium-induced testicular damage

Acute and chronic cadmium exposure causes structural and functional defects in the male reproductive system including germ cell death, inhibition of testicular steroidogenesis, testis

necrosis, and prostate cancer (Arafa et al. 2014, Erbogga et al. 2016, Ren et al. 2012). These effects may be attributed to the ability of cadmium to pass the blood testes barrier leading to alteration of the hypothalamic-pituitary-testicular axis, induction of oxidative stress, inflammatory cytokines, DNA damage, and apoptosis of germ cells (Abdelrazek et al. 2016, Wang et al. 2008). Furthermore, studies have linked reduced male fertility, such as reduced sperm count and poor semen quality, in men exposed to cadmium and/or other environmental toxicants (Benoff et al. 2000).

2. The link between Oxidative stress and inflammation pathways

2.1. Cadmium-induced oxidative stress

The main factors involved in cadmium-induced tissue injury are oxidative stress and inflammation (Arafa et al. 2014). Cadmium causes an increase in the concentration of polyunsaturated fatty acids and low antioxidant capacity that results in an alteration in the redox balance in macrophages and excessive production of ROS (Aitken et al. 2011).

Free radicals like superoxide anions generated by endogenous or exogenous sources are converted to hydrogen peroxide by superoxide dismutase (SOD). The hydrogen peroxide is further broken down to the water and molecular oxygen by either catalase (CAT) or glutathione peroxidase (GSH-Px). Glutathione reductase (GR) and GSH-Px work together to maintain a balance in glutathione (GSH) and its reduced product (GSSG). The presence of cadmium in cells interferes with these reactions by decreasing SOD, GSH and CAT thereby producing OH radicals by Haber-Weiss and Fenton reactions and accumulating free radicals. (Das et al. 2019).

2.2. Cadmium-induced inflammation

There is a physiological link between inflammation and oxidative stress wherein one may be induced by the other. Through ROS generation, cadmium increases the protein level of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which activates

nuclear factor kappa B (NF- κ B) and cyclooxygenase-2 (COX-2), creating an inflammatory microenvironment (Wang et al. 2018). Additionally, TNF- α is involved in testicular pathophysiology (Agarwal & Said 2005). It induces inducible nitric oxide synthase (iNOS) leading to an increase in nitric oxide and generation of peroxynitrite radicals that causes further cell damage by oxidizing and nitrating cellular macromolecules.

The increase in TNF- α levels is also associated with COX-2 induction and promoting the production of inflammatory prostaglandins which cause further tissue injury (Habib et al. 2019). Finally, cadmium toxicity results in oxidative stress or inflammation which may lead to the other as a secondary response. Key events include weakened antioxidant defense, elevated ROS production, activated NF- κ B and release of cytokines (Das et al. 2019).

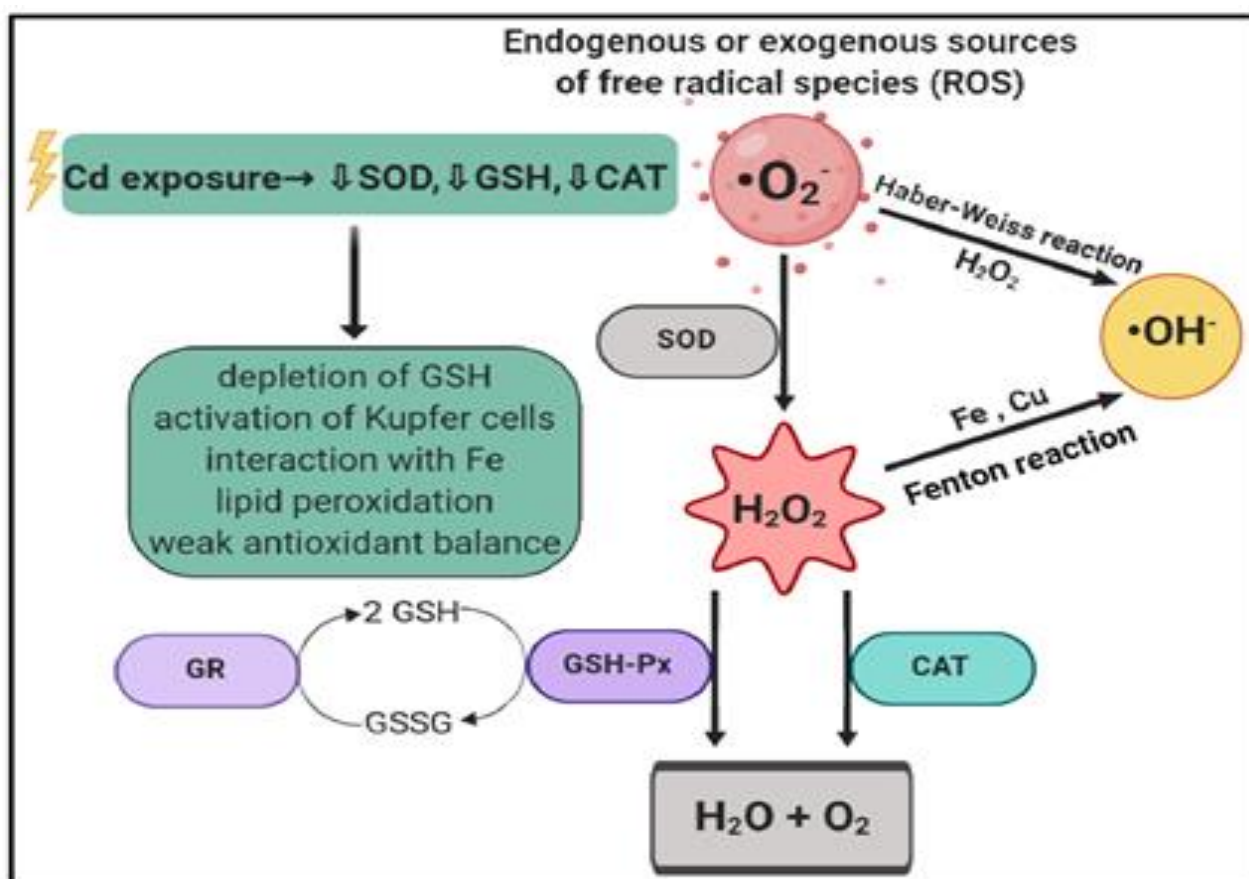


Figure 2. Effect of cadmium exposure on redox balance in the cells (Das et al. 2019).

3- Management of testicular damage

There are different therapeutic agents used in management of Cd-induced testicular damage such as natural products and monoclonal antibodies. Previous studies showed that kolaviron and quercetin have protective effects on cadmium-induced testicular damage and endocrine pathology in rats by their anti-oxidant activity (Farombi et al. 2012). Moreover, Fenugreek seed powder mitigates cadmium-induced testicular damage and hepatotoxicity in male rats by its anti-oxidant and anti-inflammatory activities (Arafa et al. 2014).

On the other hand, Infliximab, anti-TNF- α , abrogates cadmium-induced testicular damage and spermotoxicity via enhancement of steroidogenesis

and suppression of inflammation and apoptosis mediators (Habib et al. 2019).

Conclusion:

Cadmium exposure causes testicular damage by inducing oxidative stress and inflammation. Oxidative stress is characterized by an imbalance in the production of ROS and antioxidants in the organ, causing cellular disruption.

Sustained oxidative stress can trigger inflammation by activating the transcription of NF- κ B that induces production of inflammatory mediators like TNF- α . Therefore, reducing inflammation and oxidative stress is the main target to manage cadmium-induced testicular damage.

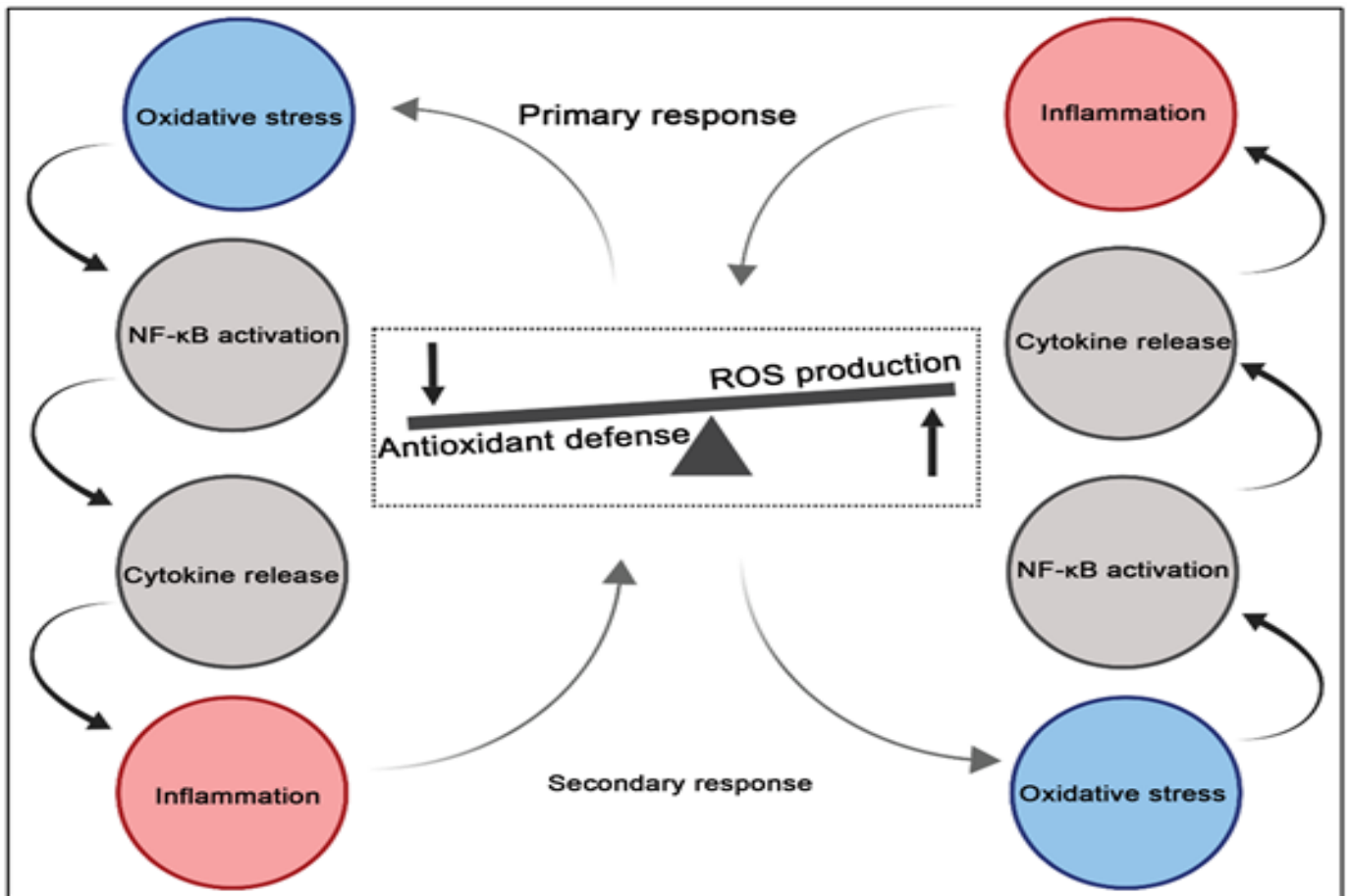


Figure 3. The link between oxidative stress and inflammation due to cadmium exposure (Das et al. 2019).

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