Animal Reproduction Science 155 (2015) 1–10

Contents lists available at ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

Review article

Toxic effects of cadmium on testis of birds and mammals: A review

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ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form 18 January 2015
Accepted 22 January 2015
Available online 31 January 2015

Keywords:
Cadmium
Toxicity
Testis
Mammals
Birds

ABSTRACT

In humans and other mammals, cadmium (Cd) causes various damages to different organs and tissues of the body. This review presents a comprehensive overview on the effect of Cd on the structure of seminiferous tubules, Leydig cells and blood vessels in the testis. The main observation of the effect of Cd is destruction of the seminiferous tubules with severe necrotic areas. Damage is to all stages of developing germ cells by inducing their structural changes and the apoptotic cell death. Sertoli supporting cells are considered the most vulnerable cells. Their damage results in cytoplasmic rearrangement and disruption of inter-Sertoli tight junctions resulting in increased permeability of the blood-testis barrier, structural changes in the Leydig cells and decreased testosterone secretion. After long time of Cd exposure an increase of the amount of interstitial connective tissue occurs. In blood vessels Cd exposure causes various morphological and physiological changes in vascular endothelial cells and smooth muscle cells. In humans and other mammals, the range of effect depends on the dose, route, ways, and duration of exposure. After necrosis of the sensitive cells Cd produced lesions in surrounding tissue and activate free cells. Atrophy of the seminiferous tubules is followed by Leydig cell regeneration and interstitial revascularization. In birds, spermatogenic cells underwent irreversible degeneration or atrophy of seminiferous tubules in the absence of significant vascular lesions.

Contents

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http://dx.doi.org/10.1016/j.anireprosci.2015.01.007
0378-4320/

1. Introduction

Cadmium (Cd) is a common environmental pollutant associated with many industrial processes. The human population and animals are exposed to Cd via contaminants found in air, drinking water and food and accumulated slowly in the body (WHO, 2000; ATSDR, 2008; Järup and Akesson, 2009). For the majority of animal species tested, the absorption of Cd can range from 0.5% to 3.0%, while in humans from 3.0% to 8.0% of the dose administered (Järup et al., 1998). Only about 1–2% of an acute Cd dose is taken up by the testes. Factors influencing the uptake are chemical components of the diet, the body's nutritional status, age and gender proportionally to dosage used and time exposure to Cd (Sarkar et al., 2013). It has a long biological half-life (~20–40 years in humans) and it accumulates in the body over a considerable period of time. Various organs can accumulate Cd, mostly liver and kidneys (WHO, 2000; Sarkar et al., 2013). After absorption Cd is transported by blood and stored in organs rich in metallothionein, which exhibits high binding affinity for Cd (Waalkes and Klaassen, 1985).

Exposure to Cd has been associated with numerous harmful effects. Structure and physiological and biochemical functions of various organs including the kidneys, liver, lung, pancreas, testis, placenta, and bone can also be connected to Cd action (ATSDR, 1999; Obianime and Roberts, 2009; Sarkar et al., 2013). The direct cytotoxic effects can lead to apoptotic and/or necrotic events. Low dose of Cd changed the immunological microcircumstances in the testis resulting in increased susceptibility to testicular autoimmunity (Ogawa et al., 2013). Potential carcinogenic effects in target organs in various animals and in humans may be ascribed to Cd (IARC, 1993; Waalkes et al., 1992; Waalkes, 2000; Huff et al., 2007). The exposure to Cd induces of decreased measures of reproductive performance including fertility, abnormal embryonic development, prenatal death, and sexual dysfunction. In animals, cadmium crosses the placenta. During later pregnancy, higher doses cause severe placental damage and fetal death. In animals exposed to cadmium prior to and during gestation, skeletal abnormalities have been reported (ATSDR, 1999). Non-toxic dose of Cd alters gene expression in mouse testes (Zhou et al., 2004) and has potent estrogen- and androgen-like activities in vivo and in vitro, by directly binding to estrogen and androgen receptors (Takiguchi and Yoshihara, 2006). Aim of the present review is to provide current knowledge on Cd effects on germinal and supporting Sertoli cells of seminiferous tubules and Leydig endocrine cells. Special attention was paid to effect of Cd on endothelial cells and smooth muscle cells of blood vessels and their involvement in possible testicular regeneration (Fig. 1).

2. Effect of Cd on germinal epithelium

First reports indicating that Cd has severe toxic effect on rat testis were published by middle of last century (Parizek and Zahor, 1956; Kar and Das, 1960; Mason et al., 1964; Chiquoine, 1964; Clegg and Carr, 1967). The exposure to Cd chloride administered via intraperitoneal or subcutaneous injection induced edema, and hemorrhagic inflammation (Gunn et al., 1963; Mason et al., 1964; Fende and Niewenhuis, 1977; Aoki and Hoffer, 1978; Nolan and Shaikh, 1986). Testicular morphology was greatly altered 3 months after initial Cd exposure, with degenerated seminiferous tubules, abnormal Leydig cells, fibrosis, and reduced testicular size (Niewenhuis, 1980). Later, many studies in man and in various species of mammals showed that Cd induces various changes in testicular histopathology. Acute Cd-induced damage to testes manifests itself by hemorrhagic inflammation, degeneration and dysfunction of the organ, vacuolization of seminiferous tubules. A marked reduction of seminiferous tubular diameter after the high dose of Cd, along with the conspicuous decrease of the tubular volume density was reported (De Sousa Predes et al., 2010). Microscopical changes were observed in the germinal epithelium like necrosis, irreversible degeneration of germinal cells and progressive sloughing of germ cells from the basement membrane (Xu and Jiang, 1996; Xu et al., 1996; Yan et al., 1997; Zhou et al., 1999; Li et al., 2000; Toman et al., 2002; Goyer et al., 2004; Obianime and Roberts, 2009; Bekheet, 2010). Repeated injections of low doses of Cd also impair spermatogenesis. The intake of low, oral doses of Cd chloride over a long period of time induces quantitative changes in apoptosis of the seminiferous epithelium of the rats, without noticeable morphologic or proliferative alterations (Herranz et al., 2010). A strong positive relationship between the percentage of apoptotic germ cells and the Cd concentration in a testis biopsy have been found (Xu et al., 1996). All testicular germ cell populations can by affected by Cd. This includes a decrease in number of spermatogonia and spermatocytes, aberrant morphology in all developing stages, release of immature cells into the lumen (Aoyagi et al., 2002; Zhou et al., 2004; Marettová et al., 2010) and failure in spermiation (Hew et al., 1993b). Cadmium chloride induce mis-orientation and loss of cell polarity in developing spermatids prior to their premature depletion from the seminiferous epithelium in adult rats (Mruk and Cheng, 2011). Differences in sensitivity to Cd in different spermatogenic cells have been recorded.

First studies in fowl (Ericson and Pincus, 1964) showed that testes, after Cd intake were not affected. Testicular hypoplasia and loss in testicular mass was one of the most obvious lesions produced by dietary Cd (Richardson et al., 1974). In the domestic pigeons a decrease of