MEDICINE AND PHISIOLOGY

TESTICULAR CHANGES UNDER THE INFLUENCE OF CADMIUM IN COMBINATION WITH METAL SUCCINATES: MODERN VIEW OF THE PROBLEM (LITERATURE REVIEW)

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Annotation. *Now an increasing number of studies indicate that male fertility, primarily spermatogenesis and ejaculate parameters, is adversely affected by an increase in environmental pollution with hazardous technogenic toxicants, among which heavy metals, in particular, cadmium, occupy a priority position. Continuous sources of cadmium contamination are associated with industrial production, nickel-cadmium batteries, pigments, plastics and other synhetic products.*

Most research scientists believe that cadmium-associated disorders of the functional activity of the hypothalamic-pituitary-gonadal system in men are manifested by a violation of both hormonal regulation of the reproductive system and the functioning of the epitheliospermatogenic layer of the seminal glands, causing pathological changes in both the quantitative and qualitative composition of sperm. Cadmium induces lipid peroxidation and reduces the activity of antioxidant enzymes, causes degenerative and destructive changes in the spermatogenic epithelium, abnormal changes in the morphological structure of sustentocytes, thereby creating favorable conditions for disturbances in the morpho-functional organization of the blood-testicular barrier and spermatogenesis. Cadmium disrupts the development and function of interstitial endocrinocytes, induces damage to their genome, enhances apoptosis of Leydig cells and causes degradation of the seminiferous tubules, and weakens the expression of genes associated with the production of male sex hormone.

Keywords: *cadmium, cadmium-induced testicular changes, testosterone,reactive oxygen species, male infertility, spermatogenesis.*

Relationship of the publication with planned research works. The work was performed in accordance with the theme "Morphofunctional features of organs and tissues under the influence of external and internal factors", № state registration 0120U105219.

According to world statistics, in the current century the level of infertility, which continues to maintain its leading position as a priority in andrology and gynecology,

does not show a declining trend: now in different countries around the world 8-29% of couples suffer from this disease, and in Ukraine the share of infertile marriages reaches 20%. In 48-51% of cases, the cause of infertility is a pathology of the male reproductive system [1].

The causes of male infertility are complex, and its etiology in half of all cases remains unknown. Currently, an increasing number of studies indicate that male fertility, especially spermatogenesis and ejaculate parameters, is adversely affected by increasing environmental pollution [2]. Exposure to pollutants in the perinatal period leads to abnormalities of the reproductive tract - cryptorchidism, hypospadias (socalled testicular dysgenesis syndrome), which can initiate the development of subfertility or infertility in adulthood [3].

Therefore, the purpose of analytical research in the scientific literature is to identify data on changes in testicular morphology under the influence of cadmium salts.

Cadmium, along with arsenic, lead and mercury, is a class of heavy metals that is considered one of the most common toxicants in the environment. Permanent sources of cadmium pollution are associated with its industrial production, production of nickelcadmium batteries, pigments, plastics and other synthetic products [4]. Accumulation of cadmium in the human body can cause numerous adverse effects, including renal and hepatic impairment, pulmonary edema, osteomalacia, testicular, adrenal, and hematopoietic damage [5].

Cadmium-associated disorders of the functional activity of the hypothalamic-pituitary-gonadal system in men are manifested by a violation of both hormonal regulation of the reproductive system and the functioning of the epitheliospermato-genic layer of the seminal glands, causing pathological changes in both quantitative and qualitative composition of sperm [6].

Testicles (testicles) - male gonads, in the parenchyma of which secrete tortuous seminal tubules, delineated by its own shell (spermatogenic compartment), and the interstitium located between them (steroidogenic compartment of the parenchyma). Representatives of the spermatogenic epithelium are Sertoli cells (CS), or sutenocytes, which perform a supporting, barrier, trophic, phagocytic, secretory, coordinating function and participate in endocrine relationships. Interstitial endocrinocytes, or Leydig cells (CL) in the steroidogenic compartment of the parenchyma produce male sex hormones (testosterone and its derivatives) and peptide hormone - insulinlike factor 3, which affects the differentiation of embryonic receptors in Leydig cells. inguinal region of the abdominal cavity and causes their initial omission [7].

Cadmium affects the development of Sertoli cells in both the fetal and neonatal periods. Exposure to cadmium (1-2 mg / kg) in pregnant female rodents can cause vacuolation of sustenocytes and loss of gametes in the spermatogenic epithelium of adults, inhibit proliferation, induce apoptosis and DNA damage of immature CS [8]. Sertoli cells in adults are also highly sensitive to cadmium: for example, rats treated with a single dose of 3 μmol / kg toxicant show vacuolation in the cytoplasm of sustenocytes and fragmentary condensation of chromatin in late spermatids [9]. The results of

research in the field of molecular biology indicate that cadmium causes changes in the cytoskeleton of KS-actin by influencing the expression of actin regulatory proteins Arp3 and Eps8 in vitro [10].

The "target" of cadmium toxicity is also the hematotesticular barrier (GTB), which in mammalian testes delimits the area of specialized contact between neighboring Sertoli cells of the basement membrane in the tortuous seminal tubules. Cadmium "attacks" GTB, causing defragmentation of actin sustentocytes in rodents and humans, and disrupts its function by affecting the activity of transforming growth factor β3, which, in turn, induces the transmission of p38 kinase signals MAPK - an important component of the cascade of mitogenactivating proteins 11]. The toxic effect of cadmium on the hematotesticular barrier is also realized due to its effect on focal adhesion kinase - nonreceptor protein tyrosine kinase of GTB regulation, which alters the activity of proteins, in particular, occludin and ZO-1, in the testes [12].

Cadmium also has a negative effect on spermatogenesis. The results of research by the author's team under the leadership of Cupertino MS et al. (2017) showed that male rodents that were exposed to the toxicant daily (0.67–1.1 mg / kg) for 7 days demonstrated disorganization of the spermatogenic epithelium of the tortuous seminal tubules [13]. According to Nna V.U. et al. (2017), after four weeks of oral administration of cadmium at a dose of 5 mg / kg, the number of sperm, their motility and viability for 28 days were significantly reduced [14].

The toxic effect of cadmium is manifested in relation to the activity of mature sperm: as noted by Zhao et al. (2017), after treatment of human and mouse sperm in vitro with this toxicant significantly reduced its motility and significantly reduced the rate of in vitro fertilization of the egg and delayed early embryonic development in mice, suggesting the epigenetic effect of the toxicant [15].

Strong evidence of a correlation between high cadmium levels in semen and male infertility was provided by a metaanalysis by Zhang Y. et al. (2019) [9]. Analysis of the causes of infertility (501 cases) in Rockville, United States, showed the presence of abnormally high levels of toxicant in the serum of adult men of these couples [16]. An assessment of urinary markers of oxidative stress, sperm quality, and arsenic, cadmium, and lead levels in the urine of 1,020 men was performed by He Y. et al. (2020) indicates that high concentrations of these toxicants adversely affect sperm quality, but show a positive correlation with elevated levels of oxidative stress markers [17].

Cadmium also causes pathological changes in the male endocrine system. Thus, Chen C. et al. (2016) reported that there is a positive correlation between the concentration of cadmium in the blood and the level of SHBG (Sex hormonebinding globulin) - a globulin that binds sex hormones [18]. Kresovich J.K. et al. (2015) based on the results of the analysis of the male population (according to the National Health and Nutrition Survey (NHANES) 1999-2004 on the content of cadmium and SHBG in the blood) also found that the concentration of this toxicant in the blood is positively associated with SHBG [19].

The authors of a number of experimental studies have established the mechanisms

of cadmium-induced endocrinocyte-damaging effects associated with the toxic effects of cadmium on interstitial Leydig cells (CL) in the steroidogenic compartment of the parenchyma. It is known about the existence of two populations of CL in rodents: Leydig fetal cells (FCL) and adult Leydig cells ("adult" CL, DCL). Shima Y. et al. (2015) note that FCLs undergo apoptosis over time and gradually disappear, although some of them persist in the "adult" testis [20].

They play an important role in the development of the male reproductive tract, producing male sex hormones and insulinike factor 3 (IPF3). Testosterone promotes the development of both internal and external genitalia of the male fetus, the development of the Wolffian duct and the vas deferens, and IPF3 causes the initial lowering of the testicles, regulating the shortening of the gubernaculum [21].

DCLs appear at the end of the second week after birth in mice and rats and increase the expression of some CL-steroidogenic enzymes, in particular the cytochrome P450 side chain cleavage enzyme (Cyp11a1) and 3β-hydroxysteroid dehydrogenase. In addition, DCLs also increase the expression of luteinizing hormone receptor, highdensity lipoprotein receptor (Scavenger receptor class B type 1, Srb1) and steroidogenic acute regulatory protein (StAR) [22].

Cadmium has an adverse effect on the development and function of DCL. In particular, the results of research by the author's team led by Wu H. et al. (2017) showed that in adult male rats exposed to cadmium 0.5 or 1.0 mg / kg, there was a significant delay in CL regeneration, lower testosterone levels and regulated decreased expression of Srb1, Star, Cyp11a1 and Cyp17a1. Subsequent in vitro studies have shown that cadmium also reduces the synthesis of male sex hormone and DNA integrity of Leydig cells [23].

There is growing evidence that the mechanism of Cd-induced male fertility disorders is related to the production of reactive oxygen species (ROS) in the testes. ROS homeostasis is supported by the production of hydroxyl, peroxyl and hydroperoxyl radicals, etc. and an antioxidant defense system. Violation of this homeostasis also leads to oxidative stress, which interferes with the development and functioning of sperm and somatic cells or induces their apoptosis [24].

Cadmium induces ROS generation in the testis. Exposure to the toxicant at a dose of 6.5 mg / kg on adult rats for 5 days initiates oxidative stress, causing increased lipid peroxidation and decreased levels of catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase, thus glutathione reductase, thereby associatedX-protein and tumor necrosis factor-α and weakening the expression of the antiapoptotic gene Bcl2 in the testis [25].

Mahmoudi R. et al. (2018) noted that in rats exposed to cadmium at a dose of 1.5 mg / kg for 13, 25 and 39 days, there was an increase in ROS production, narrowing of the tortuous seminal tubules, a decrease in spermatogonia, sustenocytes and Leydig cells, and also reduced motility and sperm count and inhibition of testosterone synthesis [26].

The effect of cadmium on adult male rats after administration of a single dose of 2 mg / kg during the day induces ROS generation and reduces the activity of superoxide dismutase and catalase in the testis, thereby destabilizing the hematotesticular barrier

and ascorbic acid, which can cause inhibition of activation of transforming growth factor β3 and phosphorylation of p38 MAPK kinase. It was also shown that rats exposed to the toxicant 3 mg / kg once a week for 28 days developed narrowing of the tortuous seminal tubules and depletion of sperm, an increase in multinucleated giant cells and degeneration of Leydig cells on the background of abnormally low activity. superoxide dismutase, catalase and glutathione [27].

The in vitro system also reliably demonstrates the ability of cadmium to induce ROS production in various testicular cells. An in vitro study of the KS germ cell subculture has shown that cadmium-induced oxygen formation reduces glutathione levels, causing cytochrome c release, caspase-3 activation, and Sertoli cell apoptosis [28].

Exposure of 10 –160 μM cadmium to Leydig cellderived rat R2C cell tumors also caused mitochondrial damage and decreased Star expression for 24 hours, after which it inhibited steroid secretion, presumably by increasing ROS levels and decreasing SOD2 activity [28]. In addition, the toxicant effect on Leydig cells of TM3 mice was manifested by a decrease in the activity of SOD2 and glutathione in the redoxsensitive Nrf2 / ARE signaling system, which plays a leading role in maintaining intracellular homeostasis under oxidative stress, thereby inhibiting production.

Although interesting epigenetic effects after cadmium exposure are observed primarily in the germ line [15], environmental-induced epigenetic changes associated with infertility are also described in somatic cells (including Sertoli cells and Leydig cells) that support spermatogenesis.

Given that the key mechanism for the development of cadmium-induced testicular injury is associated with the production of reactive oxygen species, all antioxidants, in particular vitamin C [27], vitamin E, Fragaria ananassa extract [25], cyanidin-3-O-glucoside [28], quercetin [14] and green tea [26] should partially or completely eliminate gonadotoxic effects mediated by the negative effects of cadmium.

Conclusions. Thus, the connection between the accumulation of cadmium in the body and the state of reproductive function of men deserves special attention, because the problem of male infertility with each passing year acquires special medical and social significance around the world. The accumulation of the toxicant in the testes and prostate gland is manifested by a violation of both hormonal regulation of the reproductive system and the functioning of the epitheliospermatogenic layer of the seminal glands, causing a deterioration in the production of quantity and quality of sperm.

Prospects for further research. A promising direction for the prevention and correction of the manifestations of Cd-induced testicular changes can also be considered the search and further use of cadmium bioanthogonists. A prerequisite for this assumption is the results of the work of a number of Ukrainian scientists, who proved the modifying effect of metal succinates on embryotoxicity and cardiotoxicity of cadmium salts in the experiment.

Given the above, experimental study, analysis and evaluation of the spectrum of morphological changes in the testes induced by cadmium accumulation, and the search for new bioantagonists to prevent and correct the manifestations of cadmium-induced

testicular changes, we considered relevant and promising direction of further research.

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