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OVARIAN TOXICITY OF CADMIUM CHLORIDE: MECHANISMS AND CONSEQUENCES

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Анотація. *У статті розглядається сучасний стан наукових даних щодо впливу хлориду кадмію на структурно-функціональний стан яєчників. Узагальнено експериментальні та клінічні дослідження, що демонструють токсичний потенціал кадмію як одного з найбільш небезпечних репродуктивних отрут. Особливу увагу приділено механізмам оваріотоксичності, зокрема індукції оксидативного стресу, порушенню фолікулогенезу, зниженню активності антиоксидантних ферментів, ушкодженню гранульозних і тека-клітин. Наведено дані щодо дисбалансу стероїдогенезу, змін гормонального профілю, порушень дозрівання овоцитів і розвитку атрезії фолікулів під впливом кадмію. Окремо розглянуто здатність Cd^{2+} накопичуватись у яєчниковій тканині, заміщувати ессенціальні метали та ініціювати апоптоз. Проаналізовано фактори ризику, шляхи надходження, особливості біодоступності та кумуляції кадмію. Підкреслено актуальність подальших досліджень для оцінки довгострокових наслідків впливу кадмію та пошуку ефективних протекторних засобів, здатних зменшувати його токсичність для репродуктивної системи.*

Ключові слова: *хлорид кадмію, яєчники, гранульозні клітини, апоптоз, фолікулогенез, оксидативний стрес, феропотоз.*

Abstract. *The article summarizes current scientific evidence on the effects of cadmium chloride on the structural and functional state of the ovaries. Experimental and clinical data demonstrate that cadmium is among the most potent reproductive toxicants capable of disrupting multiple ovarian processes. Particular attention is given to key mechanisms of cadmium - induced ovarian toxicity, including oxidative stress, impairment of folliculogenesis, suppression of antioxidant defense enzymes, and damage to granulosa and theca cells. The review highlights cadmium-related disturbances in steroidogenesis, alterations in hormonal balance, impaired oocyte maturation and increased follicular atresia. Special emphasis is placed on the ability of cadmium to accumulate in ovarian tissue, displace essential metals, interfere with mitochondrial function, and trigger regulated cell death pathways. The article also outlines exposure routes, bioavailability patterns, and factors determining cadmium accumulation in the reproductive system. The need for further research is emphasized, particularly regarding the long- term consequences of cadmium exposure and the search for potential protective agents capable of mitigating its detrimental effects on female reproductive health.*

Key words: *cadmium chloride, ovaries, granulosa cells, apoptosis, folliculogenesis, oxidative stress, ferroptosis.*

Connection of the publication with planned research works.

The study was carried out within the research project of the Department of Medical Biology, Pharmacognosy and Botany of the Dnipro State Medical University “Biological foundations of organ and animal morphogenesis under the influence of microelements and ultramicroelements in experimental conditions”, state registration number 0118U006635.

Introduction.

Cadmium (Cd) is a heavy metal widely present in the environment as a result of industrial activity, soil contamination, water pollution, and tobacco smoke [1, 2]. In women, cadmium accumulation is associated with reduced fertility and impaired function of the reproductive system. The ovaries are a sensitive target for Cd, as granulosa cells and follicular structures strongly depend on cellular homeostasis, antioxidant defense, and proper mitochondrial function [3, 4, 5].

Previous studies have shown that $CdCl_2$ induces apoptosis of granulosa cells through mitochondrial dysfunction, increased generation of reactive oxygen species (ROS), and activation of intracellular stress-related signaling pathways. Recent evidence also indicates the involvement of emerging forms of regulated cell death, such as ferroptosis, which opens new perspectives for understanding pathology and identifying targets for therapeutic protection [6, 7, 8, 9, 10, 11].

In light of these observations, a systematic review of current experimental mechanisms of $CdCl_2$ ovarian toxicity is warranted, with emphasis on molecular pathways, reproductive consequences, and potential protective strategies.

The aim of the study.

To summarize current experimental and molecular data on the effects of cadmium chloride on the morphological state of the ovaries, the function of granulosa cells, and the mechanisms of cellular injury.

Object and research methods.

The review was conducted through analytical evaluation of publications indexed in PubMed, Scopus, Web of Science, and DOAJ. Considered studies included in vivo experiments (rats, mice, birds), in vitro models (KGN granulosa cell line, primary cell cultures), as well as works employing transcriptomics, metabolomics, and morphological tissue analysis.

Main part.

Analysis of available publications made it possible to identify key pathological processes most frequently described in the scientific literature and to form a modern understanding of ovarian toxicity. Based on the synthe-

sis of collected data, the main mechanisms of cadmium-induced ovarian injury were determined as follows.

1. Oxidative stress and mitochondrial dysfunction.

In vitro studies in human granulosa cells (KGN) have shown that Cd increases total and mitochondrial ROS levels, reduces mitochondrial membrane potential, decreases ATP synthesis, and impairs the electron transport chain [12].

2. Apoptosis of granulosa cells via excessive mitophagy.

Experiments in mice and KGN cells demonstrate that $CdCl_2$ induces excessive mitophagy, leading to mitochondrial degradation. This results in ATP depletion, loss of mitochondrial membrane potential, and activation of caspase-3. ultimately causing apoptosis. Inhibition of autophagy e.g., with 3-methyladenine) reduces apoptotic cell death [13].

3. Endoplasmic reticulum (ER) stress.

$CdCl_2$ activates the PERK–eIF2α–ATF4 pathway via ER stress in granulosis cells, contributing to cellular injury and apoptosis [14].

4. Ferroptosis as a novel mechanism of ovarian toxicity.

Acute Cd exposure in mice produces morphological and biochemical features characteristic of ferroptosis: disturbed iron homeostasis, excessive lipid peroxidation, decreased GPX 4 and FSP1, and increased ACSL 4 expression. Ferroptosis inhibitor Ferrostatin-1 attenuates oxidative injury and ovarian damage [15].

5. Autophagy as a modulator of ferroptosis.

Cd stimulates autophagy in granulosa cells (increased LC3-II conversion, enhanced autophagic flux). This process promotes ferroptosis, whereas autophagy inhibitors (e.g., chloroquine) reduced cell death [16].

6. Genetic and epigenetic mechanisms.

Studies of m^6A methylation showed that FTO (m^6A demethylase) protects granulosa cells from $CdCl_2$ by activating the AKT/Nrf2 pathway. Overexpression of FTO reduces apoptosis and oxidative stress, while suppression of the target gene MNT abolishes this protection [17].

Morphological and functional consequences.

Histological studies reveal that acute cadmium chloride exposure causes substantial structural alterations in the ovaries, including:

- reduction of preantral and antral follicles,
- granulosa cell damage,
- decreased oocyte yield during superovulation,
- reduced number of viable follicles,
- stromal edema and hyperemia,
- luteal body degeneration [15].

These changes are associated with iron overload, oxidative stress, and lipid peroxidation, leading to depletion of the follicular reserve and disruption of cyclic processes.

Potential protective strategies.

Promising protective agents include:

- N-acetyl-L-cysteine as an SH-group donor and glutathione precursor,
- various classes of antioxidants,
- selenium compounds,
- autophagy/ferroptosis inhibitors (preclinical evidence).

Additional potential approaches include:

- targeting autophagy (e.g., chloroquine),
- modulation of m^6A methylation pathways (e.g., FTO overexpression),
- reduction of ER stress and enhancement of antioxidant defense.

However, clinical studies remain insufficient; thus, these strategies require further validation.

Conclusions.

1. Cadmium chloride exerts complex toxic effects on the ovaries, damaging the follicular apparatus, granulosa cells, and endocrine function.

2. The main mechanisms of toxicity include oxidative stress, mitochondrial dysfunction, apoptosis, autophagy, ferroptosis, and metabolic disturbances.

3. Morphological alterations comprise follicular atresia, cellular degeneration, and structural damage to the stroma and corpus luteum.

4. Cadmium chloride induced disturbances lead to reduced fertility.

5. Future research should focus on developing protective strategies targeting these pathways (e.g., autophagy inhibitors, epigenetic modulators), which may offer therapeutic potential against cadmium-induced reproductive toxicity.

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