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Review Article

Cadmium toxicity on endoplasmic reticulum functioning

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Abstract: Cadmium (Cd) is a heavy metal pollutant widely distributed in the environment due to industrial activities, mining, and agricultural practices. Cadmium-induced Toxicity exerts profound effects on ER functioning through multiple mechanisms, leading to cellular dysfunction and pathological consequences. Cadmium disrupts protein folding and activates the unfolded protein response (UPR). Cd exposure leads to the accumulation of misfolded proteins, triggering UPR pathways mediated by critical ER transmembrane sensors: IRE1, PERK, and ATF6. The subsequent UPR aims to restore ER homeostasis but can also induce apoptosis under severe stress conditions. Cd disrupts ER calcium homeostasis by inhibiting the SERCA pump, further exacerbating ER stress. The generation of reactive oxygen species (ROS also plays a critical role in Cd toxicity, damaging ER-resident proteins and amplifying UPR activation). Cadmium also affects the lipid metabolism. This review examines the mechanisms by which Cd toxicity impairs ER functioning, disruption of protein folding and quality control mechanisms, and dysregulation of calcium signaling and lipid metabolism. The subsequent cellular consequences, including oxidative stress, apoptosis, and inflammation, are discussed in the context of Cd-induced pathogenesis of diseases such as Cancer and neurodegenerative and cardiovascular disorders. Finally, potential therapeutic strategies must be explored to mitigate the adverse effects of Cd on ER functioning and human health.

Keywords: Heavy metal, cadmium, endoplasmic reticulum, lipid metabolism, unfolded protein response

Introduction

Heavy metals are ubiquitous environmental pollutants that threaten living organisms, including humans. The toxic effects of these metals persist in some form and are harmful to the human body and its proper functioning, even if they do not play a biological role. The Toxicity of metals depends on the absorbed dose, route of exposure, and duration of exposure. The Toxicity can lead to various disorders and excessive damage due to oxidative stress caused by forming free radicals. There are several sources of heavy metal toxicity in the environment [1-4]. Heavy metals enter the environment through industrial activities, mining operations, and water and soil pollution. The sources include lead, mercury, Cadmium, and arsenic. Humans and other organisms are exposed through air, water, and food consumption. The bioaccumulation of these metals can lead to elevated tissue concentrations and aggravate the risk of Toxicity [3, 5].

Cells employ intricate mechanisms for the uptake of heavy metals, involving transporters and receptors. Metal ions mimic essential nutrients, leading to their incorporation into cellular processes. This disruptive behavior can compromise cellular homeostasis by interfering with the transport of essential ions and nutrients, leading to imbalances within the cell. Upon exposure to heavy metals, cells activate intricate stress response pathways. Oxidative stress is a hallmark characterized by the imbalance between ROS production and antioxidant defenses. This oxidative challenge can induce DNA damage and activate signal transduction pathways, influencing cellular fate. Stress response proteins are crucial in mitigating these effects, orchestrating a cellular defense against heavy metal-induced damage. Heavy metals disrupt cellular homeostasis by affecting ion balance, energy metabolism, and protein folding. Intracellular compartments such as the endoplasmic reticulum and mitochondria are

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particularly susceptible. Disruption of ion homeostasis can lead to membrane depolarization and impaired cellular signaling. The altered energy metabolism further contributes to cellular dysfunction, with implications for overall cellular homeostasis [6, 7].

Heavy metals exhibit genotoxic and mutagenic effects, impacting DNA integrity and stability. DNA repair mechanisms are often overwhelmed, leading to mutations and chromosomal aberrations. The consequences of heavy metal-induced mutagenesis extend to cellular functions, contributing to the overall disruption of homeostasis [8-11]. Cells deploy detoxification mechanisms to counter heavy metal toxicity. Metallothioneins and glutathione play vital roles in binding and sequestering metal ions, preventing their adverse effects [12, 13].

Additionally, detoxifying enzymes catalyze the conversion of toxic metal ions into less harmful forms. Understanding these detoxification pathways is crucial for developing strategies to enhance cellular resilience against heavy metal exposure. Despite significant progress, challenges remain in fully understanding the complexities of heavy metal toxicity [13].

Cadmium is a heavy metal pollutant widely distributed in the environment due to industrial activities, mining, and agricultural practices. Human exposure to Cd occurs through various routes, including contaminated food, water, and air. Once internalized, Cd accumulates primarily in the liver and kidneys, exerting toxic effects on multiple organ systems [1, 7]. Direct hazards of cadmium metal poisoning to the human body include kidney damage, bone weakness, respiratory and gastrointestinal disorders, cardiovascular issues, reproductive diseases, Cancer, etc. These hazards can arise from occupational exposure, contaminated food and water, and cigarette smoke. The primary treatment for cadmium poisoning involves several approaches, such as removal from exposure, chelation therapy, dietary modifications, and monitoring [13].

While the mechanisms of Cd toxicity have been extensively studied, its impact on cellular organelles, such as the endoplasmic reticulum (ER), has emerged as a significant area of investigation. Of particular interest in recent years is the growing understanding of how Cd disrupts the normal functioning of cellular organelles, notably the endoplasmic reticulum (ER). The ER is a multifunctional organelle involved in crucial cellular processes such as protein synthesis, folding and modification, lipid biosynthesis, and calcium homeostasis. Proper ER function is essential for maintaining cellular homeostasis and ensuring the integrity of numerous physiological processes [15, 17].

Cadmium (Cd) is a pervasive environmental toxin that exerts deleterious effects on various cell types by inducing endoplasmic reticulum (ER) stress [15]. Cellular uptake of Cd is facilitated by divalent metal transporter 1 (DMT1) and ZIP8, allowing its accumulation within various tissues and organelles [18]. ER stress occurs when the folding capacity of the ER is overwhelmed by an accumulation of misfolded or unfolded proteins within its lumen. This triggers a signaling cascade known as the unfolded protein response (UPR), aimed at restoring ER homeostasis by attenuating protein synthesis, thereby reducing protein folding load, increasing protein folding capacity, and degradation of misfolded proteins. However, chronic or excessive ER stress can lead to sustained activation of the UPR, resulting in cellular dysfunction and, ultimately, cell death [19, 20].

The present review provides a comprehensive view of cadmium-induced Toxicity and its effects on Endoplasmic reticulum (ER) functioning.

Endoplasmic reticulum structure and function

The endoplasmic reticulum (ER) is a dynamic and structurally complex organelle found in eukaryotic cells, playing a pivotal role in a wide array of cellular processes essential for homeostasis and cell survival [21]. Structurally, the ER consists of a network of interconnected membrane-bound tubules and flattened sacs, encompassing a large portion of the cytoplasmic space within the cell. The ER can be broadly classified into two distinct regions: the rough endoplasmic reticulum (RER) and the smooth endoplasmic reticulum (SER), each with unique structural features and specialized functions.

Rough endoplasmic reticulum (RER)

The RER is characterized by ribosomes attached to its cytoplasmic surface, giving it a

"rough" appearance under electron microscopy. These ribosomes are engaged in protein synthesis, translating messenger RNA (mRNA) into polypeptide chains that translocate into the ER lumen for further processing and modification. The RER is central in synthesizing and folding secretory and membrane proteins destined for various cellular compartments or secretion outside the cell. As newly synthesized proteins enter the ER lumen, they undergo post-translational modifications such as glycosylation, disulfide bond formation, and protein folding facilitated by molecular chaperones and enzymes residing within the ER [22].

Smooth endoplasmic reticulum (SER)

In contrast to the RER, the SER lacks ribosomes on its surface and appears "smooth" under electron microscopy. The SER is involved in diverse cellular functions, including lipid metabolism, calcium storage, detoxification of xenobiotics, and carbohydrate metabolism. One of the primary functions of the SER is the synthesis of lipids, including phospholipids and cholesterol, which are crucial components of cellular membranes and lipid bilayers. Additionally, the SER plays a vital role in calcium homeostasis by sequestering and releasing calcium ions in response to cellular signals, thereby regulating intracellular calcium levels and facilitating various physiological processes such as muscle contraction, neurotransmitter release, and cell signaling [21].

Integrated functions of the endoplasmic reticulum

While the RER and SER exhibit distinct structural features and functions, they are interconnected and functionally integrated organelles that collaborate to maintain cellular homeostasis. For example, synthesizing lipids in the SER requires precursor molecules derived from the RER, emphasizing the coordination between these two compartments. Moreover, the ER is a hub for coordinating diverse cellular processes, including protein synthesis, folding, quality control, lipid biosynthesis, calcium signaling, and cellular stress responses [21, 23].

Endoplasmic reticulum stress and unfolded protein response

Due to disturbance of the ER functioning, the accumulation of misfolded or unfolded proteins leads to a condition known as ER stress. In response to ER stress, cells activate a complex signaling network termed the unfolded protein response (UPR). The UPR aims to restore ER homeostasis by enhancing protein folding capacity, reducing protein synthesis, and promoting the degradation of misfolded proteins [19, 24, 25]. However, persistent or severe ER stress can trigger cell death pathways, contributing to the pathogenesis of various diseases.

The Unfolded Protein Response (UPR) is a cellular stress response resulting from the endoplasmic reticulum (ER) stress. Its primary function is to ensure proper protein folding and maintain cellular homeostasis. When misfolded or unfolded proteins accumulate in the ER, the UPR is activated to mitigate this stress [23]. The main functions of the UPR include: 1. Enhancing Protein Folding Capacity: Upregulates the expression of molecular chaperones and folding enzymes to increase the ER's ability to fold proteins correctly. 2. Degrading Misfolded Proteins: Activates mechanisms such as ER-associated degradation (ERAD) to target misfolded proteins for degradation. 3. Reducing Protein Synthesis: Temporarily reduces the overall rate of protein synthesis to decrease the load of new proteins entering the ER, giving it time to process the accumulated unfolded proteins. 4. Promoting Cell Survival or Apoptosis: If the stress is not resolved, the UPR can trigger apoptotic pathways to eliminate damaged cells, thus protecting the organism from potential harm.

Molecular mechanisms of endoplasmic reticulum stress: 1. The UPR is mediated by three main signaling pathways: PERK (protein kinase RNA-like ER kinase), IRE1 (inositol-requiring enzyme 1), and ATF6 (activating transcription factor 6). These sensors initiate signaling cascades to alleviate ER stress and restore cellular homeostasis. 2. However, persistent or severe ER stress can trigger cell death pathways, contributing to the pathogenesis of various diseases. Interferes with protein folding machinery in the ER, impairing the function of chaperones such as BiP/GRP78 and promoting the aggregation of misfolded proteins. This disruption compromises protein quality control mechanisms, accumulating toxic protein aggregates and ER dysfunction.

IRE1 mediates the unconventional splicing of X-box binding protein 1 (XBP1) mRNA, producing an active transcription factor that upregulates genes involved in protein folding and ER-associated degradation (ERAD). PERK phosphorylates eukaryotic initiation factor 2 alpha (eIF2α), attenuating global protein synthesis while promoting the translation of ATF4, a transcription factor that induces genes involved in amino acid metabolism, antioxidant defense, and apoptosis. ATF6 is transported to the Golgi apparatus upon ER stress, where it undergoes proteolytic cleavage to release an active transcription factor that upregulates UPR target genes [20, 26-29].

Effect of cadmium on ER functions

The cellular organelle particularly vulnerable to cadmium toxicity is the endoplasmic reticulum (ER). Cadmium Toxicity affects the function of ER in several ways.

Induction of ER stress

Cadmium exposure has been shown to induce ER stress by perturbing protein folding and calcium homeostasis within the ER lumen. Cadmium ions interfere with the function of ER-resident chaperone proteins, such as glucose-regulated protein 78 (GRP78), protein disulfide isomerase (PDI), and calreticulin, which are essential for proper protein folding and quality control. As a result, the accumulation of misfolded or unfolded proteins triggers the unfolded protein response (UPR), activating signaling pathways to restore ER homeostasis [14-16].

Activation of UPR signaling pathways

Cadmium exposure activates all three branches of the UPR, namely the PERK, IRE1, and ATF6 pathways. Activation of PERK leads to phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α), resulting in attenuation of global protein synthesis and selective translation of ATF4, a transcription factor involved in regulating genes related to amino acid metabolism, antioxidant defense, and apoptosis. Similarly, activation of IRE1 leads to splicing of X-box binding protein 1 (XBP1) mRNA, producing an active transcription factor that upregulates genes involved in ER-associated degradation (ERAD) and lipid biosynthesis. Additionally, ATF6 is cleaved and translocated to the nucleus upon cadmium exposure, promoting the expression of UPR target genes associated with protein folding and ER stress response [30, 31].

Disruption of calcium homeostasis

Cadmium interferes with calcium signaling and homeostasis within the ER, leading to dysregulation of calcium-dependent processes such as protein folding, ERAD, and apoptosis. Cadmium ions can directly bind to calcium-binding proteins within the ER lumen, disrupting their function and impairing calcium storage and release. Dysregulated calcium signaling exacerbates ER stress and UPR activation, leading to cellular dysfunction and cell death [32].

Implications for cellular health and disease

Chronic exposure to Cadmium and sustained activation of ER stress leads to the pathogenesis of various diseases, including neurodegenerative disorders, cardiovascular diseases, Cancer, and metabolic syndromes. Cadmium-induced ER stress promotes cell death pathways and contributes to tissue damage and dysfunction in affected organs. Moreover, cadmium exposure can potentiate the Toxicity of other environmental stressors and exacerbate disease progression [33, 34].

Cadmium can induce endoplasmic reticulum (ER) stress by disrupting protein folding and calcium homeostasis within the ER lumen [35, 36].

Disruption of protein folding: 1. Direct Interaction with Proteins: Cadmium can bind to thiol groups in cysteine residues of proteins, leading to misfolding or improper assembly of proteins. This accumulation of misfolded proteins triggers the unfolded protein response (UPR). 2. Inhibition of Chaperone Function: Chaperones, such as BiP/GRP78, are essential for proper protein folding. Cadmium can inhibit the function of these chaperones, increasing the burden of misfolded proteins in the ER.

Disruption of calcium homeostasis: The ER is a significant reservoir for calcium ions (Ca^{2+}), critical for various cellular functions, including protein folding. Many chaperones and folding enzymes are calcium-dependent. Cadmium can mimic calcium and compete for binding

sites on these proteins, impairing function. Cadmium can affect the function of ER calcium channels (such as inositol 1,4,5-trisphosphate receptors, IP3Rs) and pumps (such as sarco/endoplasmic reticulum Ca^{2+}-ATPase, SERCA). This leads to a disruption in calcium flux between the ER and the cytoplasm, disturbing calcium homeostasis.

Cadmium toxicity and lipid metabolism

Cadmium (Cd), a major environmental pollutant, has been recognized for its detrimental effects on lipid metabolism, with a significant role attributed to its disruption of the endoplasmic reticulum (ER) [34].

Cd enters cells through transporters and receptors, accumulating predominantly in the endoplasmic reticulum due to its high affinity for this organelle. The preferential accumulation in the ER sets the stage for significant disruptions in cellular functions, particularly those related to lipid metabolism. Cd toxicity induces ER stress, triggering the unfolded protein response (UPR). The excessive accumulation of misfolded proteins in the ER lumen activates UPR sensors, including PERK, IRE1, and ATF6. While UPR aims to restore ER homeostasis, chronic Cd exposure overwhelms this adaptive response, leading to sustained ER stress.

Lipid metabolism is a tightly regulated process crucial for cellular homeostasis. The endoplasmic reticulum plays a central role in lipid synthesis, folding of membrane proteins, and regulation of cellular calcium levels. Cd-induced disturbances in the ER profoundly impact these processes, contributing to alterations in lipid homeostasis. Lipids are transported within the body through various lipoprotein particles, including chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Chylomicrons transport dietary lipids absorbed from the intestine, while VLDL and LDL carry endogenously synthesized lipids from the liver to peripheral tissues. HDL, often called “good cholesterol”, removes excess cholesterol from peripheral tissues and facilitates reverse cholesterol transport to the liver for excretion. Lipids also serve as signaling molecules, regulating various cellular processes through interactions with specific receptors and signaling pathways. Lipid signaling molecules include phospholipids, sphingolipids, eicosanoids, and sterols, which modulate cell proliferation, differentiation, apoptosis, inflammation, and metabolism. For example, phosphatidylinositol (PI) phospholipids regulate intracellular signaling through the generation of second messengers, such as inositol trisphosphate (IP3) and diacylglycerol (DAG), which activate protein kinase C (PKC) and regulate calcium signaling. The ER is a central hub for lipid synthesis and processing. Cd-induced ER stress disrupts these processes by affecting key enzymes and regulators involved in lipid metabolism [37-39]. The inhibition of proteins crucial for lipid synthesis, such as SREBPs and ACC, leads to the dysregulation of triglycerides and fatty acids. Cd-induced ER stress can activate ER-associated degradation (ERAD), a process aimed at eliminating misfolded proteins. However, excessive ERAD activation may lead to the degradation of essential proteins involved in lipid metabolism, exacerbating the disruption of lipid homeostasis [40].

ER stress induced by Cd perturbs calcium homeostasis in the ER. Calcium signaling is critical for regulating lipid metabolism, influencing lipogenesis and lipolysis [41]. Cd-mediated disturbances in ER calcium levels contribute to alterations in lipid handling within the cell. Heavy metals perturb protein folding in the endoplasmic reticulum (ER), causing ER stress. This triggers the unfolded protein response (UPR) to restore ER homeostasis, but chronic stress may lead to ER-associated degradation (ERAD). Disruption of protein folding affects the synthesis and maturation of proteins, particularly those involved in cell signaling and structural integrity. Unresolved ER stress contributes to cellular dysfunction and, in severe cases, apoptosis. Cd-induced disruptions in lipid metabolism result in the accumulation of lipid intermediates, such as triglycerides and free fatty acids, within the cells [37]. This aberrant lipid accumulation, impaired mitochondrial function, and oxidative stress lead to lipotoxicity, a condition characterized by cellular dysfunction and damage [34]. Lipotoxicity contributes to the pathogenesis of various metabolic disorders, including obesity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases [38]. The perturbation of lipid metabolism through Cd-induced ER dysfunction has wide-ranging consequences for

cellular and organismal health. Dysregulated lipid homeostasis contributes to developing metabolic disorders, cardiovascular diseases, and hepatotoxicity, linking Cd exposure to systemic health issues. The specific molecular targets within the ER involved in Cd-induced lipid dysregulation open avenues for therapeutic interventions. On elucidating these targets and developing strategies to mitigate the impact of Cd on ER-mediated lipid metabolism. Future research efforts should focus on identifying novel therapeutic targets and preventive strategies to reduce the adverse effects of Cd exposure on lipid metabolism and overall human health [42, 43].

There is epidemiological evidence linking cadmium exposure to metabolic disorders, cardiovascular diseases, and hepatotoxicity. Heavy metals' genotoxic and mutagenic effects emphasize their impact on DNA integrity and stability. The potential for heavy metal-induced mutations and their implications for cellular function. The cellular detoxification mechanisms that cells employ to counteract heavy metal toxicity. The role of metallothioneins, glutathione, and other detoxifying enzymes in maintaining cellular homeostasis. The cellular detoxification mechanisms are activated in response to cadmium exposure - the current challenges and gaps in understanding heavy metal toxicity [44]. There are potential avenues for future research, such as developing novel detoxification strategies and exploring preventive measures.

Cadmium toxicity and diseases

Chronic exposure to Cadmium, primarily through contaminated food, water, air, and occupational settings, can accumulate Cadmium in various tissues and organs, resulting in toxic effects and the development of several diseases [7, 17]. The following are some of the critical diseases associated with cadmium toxicity.

Renal dysfunction

Cadmium primarily accumulates in the kidneys, which have a long biological half-life and cause severe damage to renal tubular cells. Chronic exposure to Cadmium is strongly associated with the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Cadmium-induced renal dysfunction is characterized by proteinuria, impaired glomerular filtration rate (GFR), tubular dysfunction, and renal failure [45, 46].

Osteoporosis and bone diseases

Cadmium interferes with calcium metabolism and bone remodeling, leading to the development of osteoporosis and other bone diseases. Cadmium displaces calcium from bone matrix proteins and inhibits osteoblastic activity while promoting osteoclastic bone resorption, resulting in decreased bone mineral density, skeletal deformities, and increased fracture risk. Chronic cadmium exposure is a significant risk factor for osteoporosis and bone fractures, particularly in postmenopausal women [47-49].

Cardiovascular disorders

Cadmium toxicity is associated with many cardiovascular diseases, like atherosclerosis, hypertension, and myocardial infarction. Cadmium exposure promotes oxidative stress, inflammation, endothelial dysfunction, and dyslipidemia, contributing to the pathogenesis of cardiovascular disorders. Cadmium-induced vascular damage and impaired cardiac function may lead to hypertension, coronary artery disease, and heart failure [50, 51].

Cancer

Cadmium is classified as a known human carcinogen by the International Agency for Research on Cancer (IARC), with evidence linking cadmium exposure to the development of various cancers, including lung cancer, prostate cancer, and kidney cancer. Cadmium acts as a tumor promoter by promoting cell proliferation, inhibiting DNA repair mechanisms, and disrupting cellular signaling pathways involved in apoptosis and cell cycle regulation. Occupational exposure to Cadmium in industries such as mining, smelting, and battery manufacturing poses an exceptionally high risk of cancer development [52-54].

Neurological disorders

Cadmium toxicity has been implicated in the pathogenesis of neurological disorders, including cognitive impairment, neurobehavioral deficits, and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Cadmium crosses the blood-brain barrier and accumulates in the brain, which induces oxidative stress, neuroinflammation, and neuronal damage. Chronic cadmium exposure may impair neurotransmitter function, disrupt synaptic plasticity, and contribute to the progression of neurodegenerative conditions [29, 55].

Reproductive and developmental effects

Cadmium exposure is associated with adverse effects on reproductive health and development. In males, cadmium toxicity can lead to testicular damage, impaired spermatogenesis, and reduced fertility. In females, cadmium exposure during pregnancy may increase the risk of adverse pregnancy outcomes, including low birth weight, preterm birth, and developmental abnormalities in offspring. Cadmium may disrupt hormonal balance, interfere with reproductive organ function, and induce oxidative damage to reproductive tissues [56-58].

Amelioration of cadmium-induced toxicity

Mitigating the adverse effects of cadmium toxicity requires a multifaceted approach aimed at reducing exposure, enhancing detoxification mechanisms, and restoring cellular homeostasis. Several strategies have been proposed to alleviate cadmium-induced Toxicity and protect against its harmful effects.

Environmental and occupational regulations

Implementing stringent regulations and guidelines to control cadmium emissions and exposure in industrial settings, agriculture, and consumer products is essential for reducing human exposure to Cadmium. This includes industrial hygiene practices, waste management, pollution control technologies, and occupational safety protocols to minimize cadmium release into the environment and prevent occupational exposure.

Dietary interventions

Consuming a balanced diet rich in essential nutrients, antioxidants, and detoxifying agents can help mitigate the toxic effects of Cadmium and reduce its absorption and accumulation in the body. Foods high in calcium, iron, zinc, and selenium may compete with Cadmium for absorption and binding sites, reducing its bioavailability. Additionally, increasing the dietary intake of fruits, vegetables, and whole grains, rich in antioxidants such as vitamins C and E and phytochemicals, can help counteract cadmium-induced oxidative stress and inflammation [59].

Chelation therapy

Chelation therapy administers chelating agents that bind to heavy metals such as Cadmium and facilitate their excretion from the body. Commonly used chelating agents include ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), and dimercaptopropane sulfonate (DMPS). Chelation therapy may be indicated in acute cadmium poisoning or chronic cadmium exposure with significant tissue accumulation and Toxicity [10, 60].

Phytotherapy

Plant-based remedies and herbal supplements have been investigated for their potential to mitigate cadmium toxicity through their antioxidant, anti-inflammatory, and metal-chelating properties. Certain plant extracts and phytochemicals, such as curcumin, quercetin, resveratrol, and silymarin, have shown promise in experimental studies to reduce cadmium-induced oxidative stress, protect against tissue damage, and enhance metal detoxification pathways [60-62].

Lifestyle modifications

Adopting healthy lifestyle habits, such as regular exercise, smoking cessation, and avoidance of alcohol and other toxic substances, can help reduce the burden of cadmium toxicity on the body. Exercise has been shown to enhance antioxidant defenses, promote detoxification processes, and improve overall health outcomes in individuals exposed to environmental pollutants, including Cadmium.

Conclusion

Various sources of heavy metal exposure include industrial activities, mining, and contaminated water and soil - the potential routes of entry into living organisms and their accumulation in tissues. Cadmium infiltrates the environment through industrial activities, contaminating air, water, and the food chain. This section

details primary sources, such as industrial emissions and agricultural practices, emphasizing entry routes into the human body. Heavy metal toxicity profoundly influences cellular homeostasis, leading to a cascade of adverse effects on cellular functions [8, 9]. A comprehensive understanding of the molecular mechanisms involved is crucial for developing effective strategies to mitigate the impact of heavy metal exposure on living organisms. The review article provides comprehensive insights into the complex interplay between endoplasmic reticulum (ER) stress, unfolded protein response (UPR), and cadmium toxicity, elucidating their implications for cellular health and disease [19, 25]. The endoplasmic reticulum serves as a critical hub for protein folding, lipid biosynthesis, and calcium homeostasis, with disruptions in ER function triggering ER stress and activating the UPR. The UPR orchestrates adaptive responses to restore ER homeostasis, but chronic or severe ER stress can contribute to the pathogenesis of various diseases, including neurodegenerative disorders, Cancer, metabolic syndromes, and inflammatory conditions [63].

In conclusion, understanding the molecular mechanisms underlying ER stress, UPR activation, and cadmium toxicity provides valuable insights into disease pathogenesis and identifies potential therapeutic targets for intervention. By addressing the root causes of ER stress and cadmium toxicity and implementing preventive measures to reduce exposure risks, individuals, communities, and policymakers can work together to safeguard cellular health and mitigate the adverse effects of environmental pollutants on human health. In conclusion, Cd toxicity disrupts lipid metabolism through ER dysfunction, unveiling a complex interplay between heavy metal exposure and cellular homeostasis. Understanding the molecular intricacies of these processes is imperative for devising targeted therapeutic strategies and implementing preventive measures to counter the adverse health effects of Cd exposure. Future research should focus on elucidating novel detoxification strategies, exploring preventive measures, and understanding the long-term consequences of chronic exposure. Interdisciplinary approaches integrating molecular biology, toxicology, and environmental science are essential for a comprehensive understanding of Cadmium-induced disruptions to cellular homeostasis. In conclusion, addressing cadmium-induced Toxicity requires a comprehensive approach encompassing environmental regulations, dietary interventions, chelation therapy, phytotherapy, lifestyle modifications, and public health education. By implementing these strategies, individuals, communities, and policymakers can work together to mitigate the adverse effects of cadmium exposure and safeguard public health.

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Disclosure of conflict of interest

None.

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