Casual Friday Series

Heavy-Hitting Heavy Metals I
Cadmium

A BIOGENETIX CLINICAL PRESENTATION

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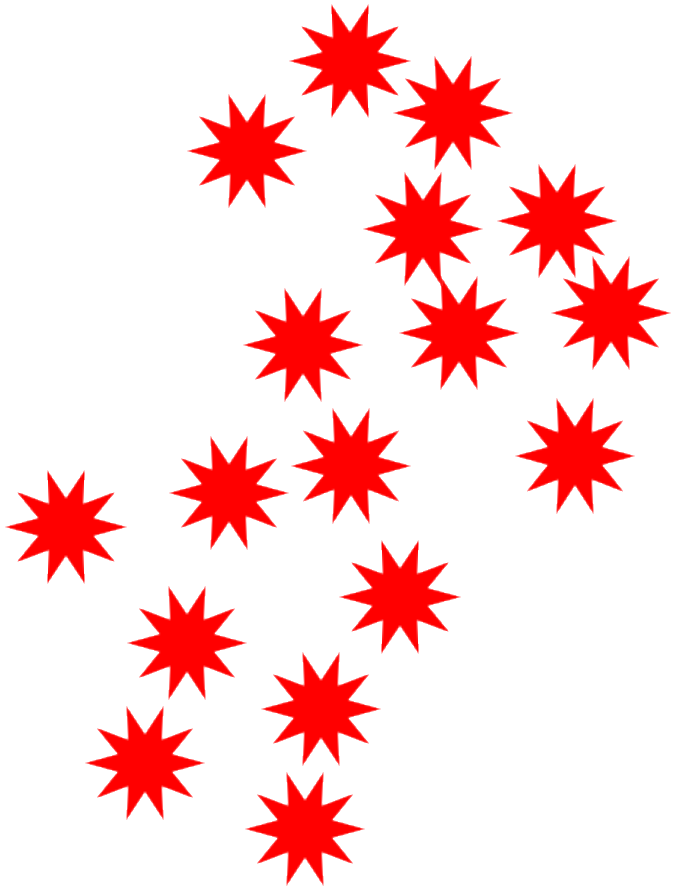
= Glucose Molecule



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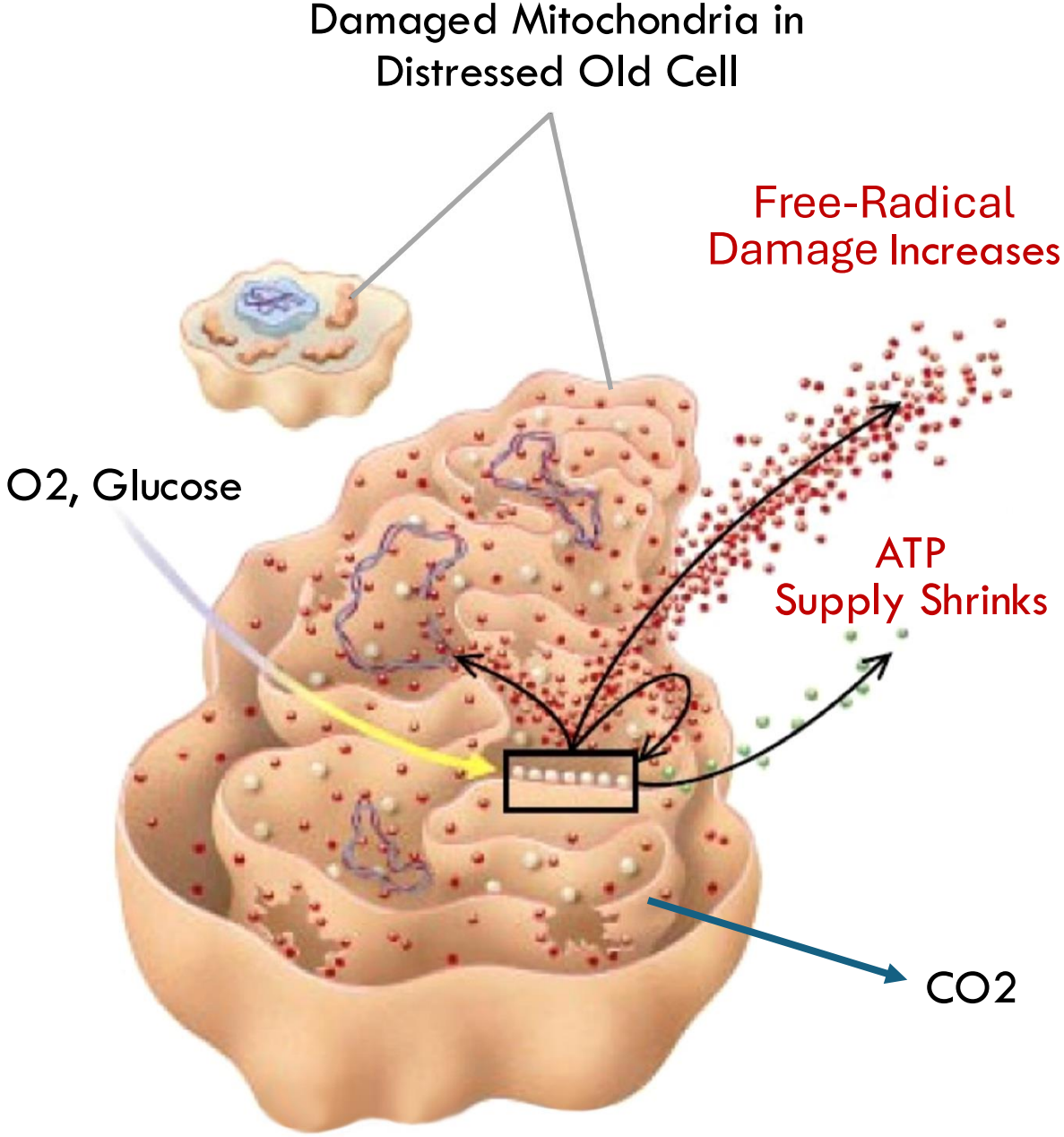

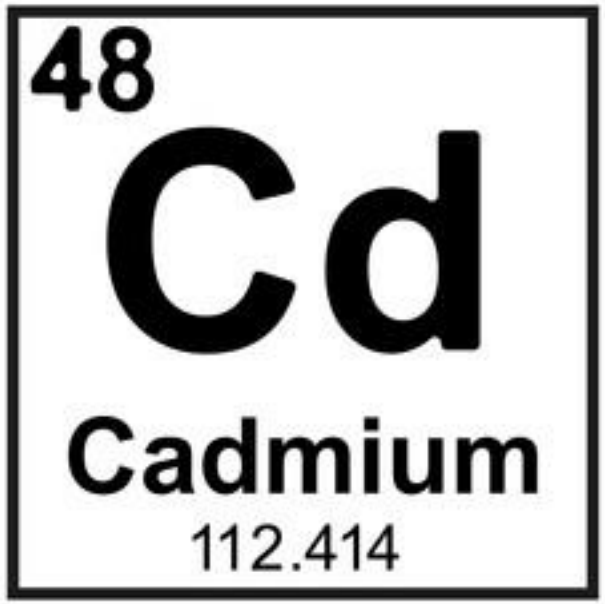

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> Toxics. 2022 Feb 23;10(3):107. doi: 10.3390/toxics10030107.

Diabetogenic and Obesogenic Effects of Cadmium in Db/Db Mice and Rats at a Clinically Relevant Level of Exposure

Jessica Nguyen [1], Arjun Patel [2], Andrew Gensburg [3], Rehman Bokhari [3], Peter Lamar [4], Joshua Edwards [4]

Overall, this study shows that Cd exposure at a level that mirrors life-long human exposure results in diabetogenic as well as obesogenic effects. Further study is needed to identify how Cd may alter leptin levels, which may adversely affect blood glucose levels. Of great interest is to determine how Cd alters bodyweight and specifically white adipose tissue weeks after the last Cd dose is administered. This research could have implications in global efforts to reduce tobacco use considering the importance of cigarettes as a source of Cd exposure and the profound effects cigarette smoke has on body weight. How important the exposure to environmental substances is in determining the likelihood of a person becoming diabetic or obese remains to be determined. However, studies such as this would indicate that exposure to environmental toxicants such as Cd certainly warrant further investigation.

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REVIEW PAPER

Cadmium: An Emerging Role in Adipose Tissue Dysfunction

Sarra Mohammed Attia[1,2] · Kavitha Varadharajan[1] · Muralitharan Shanmugakonar[1] · Sandra Concepcion Das[1] · Hamda A. Al-Naemi[1,2]

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Cadmium (Cd) is a toxic heavy metal that is widespread in the environment due to the substantial anthropogenic inputs from the agriculture and industrial sectors. The toxic impact of Cd adversely affects human health and is linked with endocrine disruption, carcinogenicity, diabetes-related diseases, and metabolic disorder. One of the main characterizations of Cd is bioaccumulation where its half-life reaches 40 years with an unknown biological role. Several organs were found to be targets for Cd accumulation such as the liver, kidneys, and adipose tissue. Adipose tissue (AT) is a dynamic organ that plays a significant role in the body's homeostasis through the maintenance of energy storage. Another vital function for AT is the secretion of adipokines which provides a metabolic cross-talk with the whole body's organs. Cd is found to adversely impact the function of AT. This includes the disruption of adipogenesis, lipogenesis, and lipolysis. As a consequence, dysfunctional AT has disruptive patterns of adipokines secretions. The main adipokines produced from AT are leptin and adiponectin. Both were found to be significantly declined under the Cd exposure. Additionally, adipose tissue macrophages can produce either anti-inflammatory markers or pro-inflammatory markers depending on the local AT condition. Cadmium exposure was reported to upregulate pro-inflammatory markers and downregulate anti-inflammatory markers. However, the exact mechanisms of Cd's adverse role on AT structure, function, and secretion patterns of adipokines are not totally clarified. Therefore, in this review, we present the current findings related to Cd detrimental effects on adipose tissues.

https://link.springer.com/article/10.1007/s12403-021-00427-3

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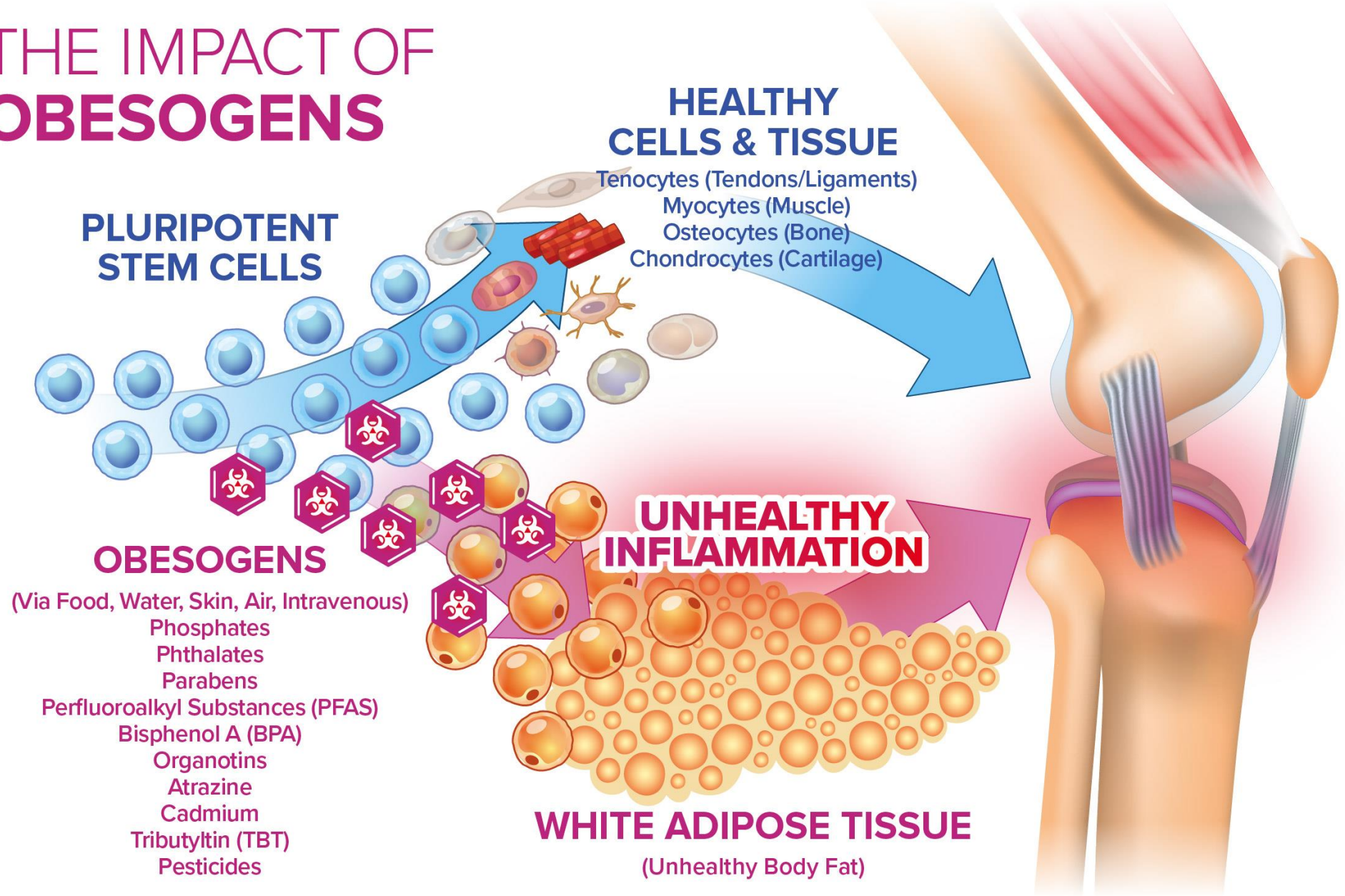
THE IMPACT OF **OBESOGENS**



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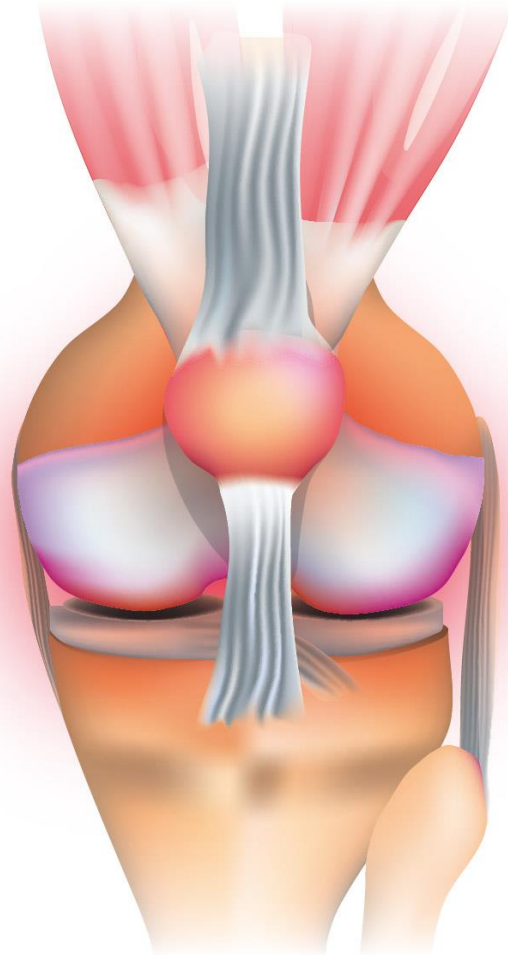
THE **ADIPOKINE** SPIRAL



1
Obesogens Drive
Stem Cells into Adipocytes

2
Adiposity Increases

3
Increased
Adipokine Activity

4
Triggering
Increased
Unhealthy Inflammation

5
Ongoing
Tissue Damage

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Adipokines

Adipokines are proteins produced by adipose tissue that can be pro- or anti-inflammatory. Some examples of adipokines include:

- **Leptin**: A pro-inflammatory adipokine that comes from adipocytes
- **Resistin**: A pro-inflammatory adipokine that comes from adipocytes and peripheral blood mononuclear cells
- **Adiponectin**: An adipokine that can be anti-inflammatory
- **Visfatin**: An adipokine that can be pro-inflammatory
- **Lipocalin-2**: A pro-inflammatory adipokine that comes from adipocytes and macrophages
- **Interleukin 6**: An adipokine that can be pro-inflammatory
- **Tumor-necrosis factor**: An adipokine that can be pro-inflammatory
- **Interleukin 10**: An adipokine that can be anti-inflammatory
- **Transforming growth factor-β**: An adipokine that can be pro-inflammatory

Adipokines can affect insulin resistance, lipid and glucose metabolism, and inflammation. An imbalance of adipokines can lead to metabolic syndrome, type 2 diabetes, and cardiovascular disease.

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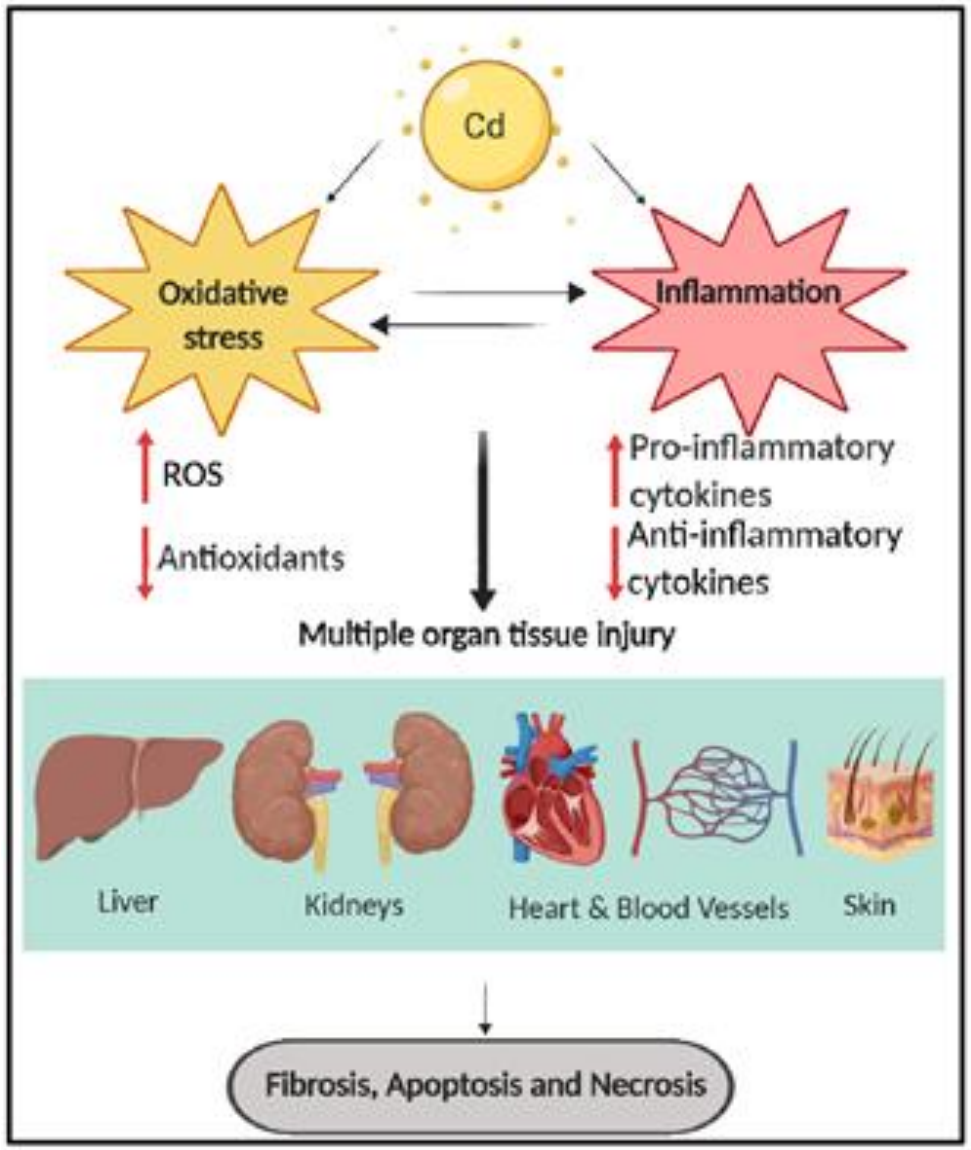
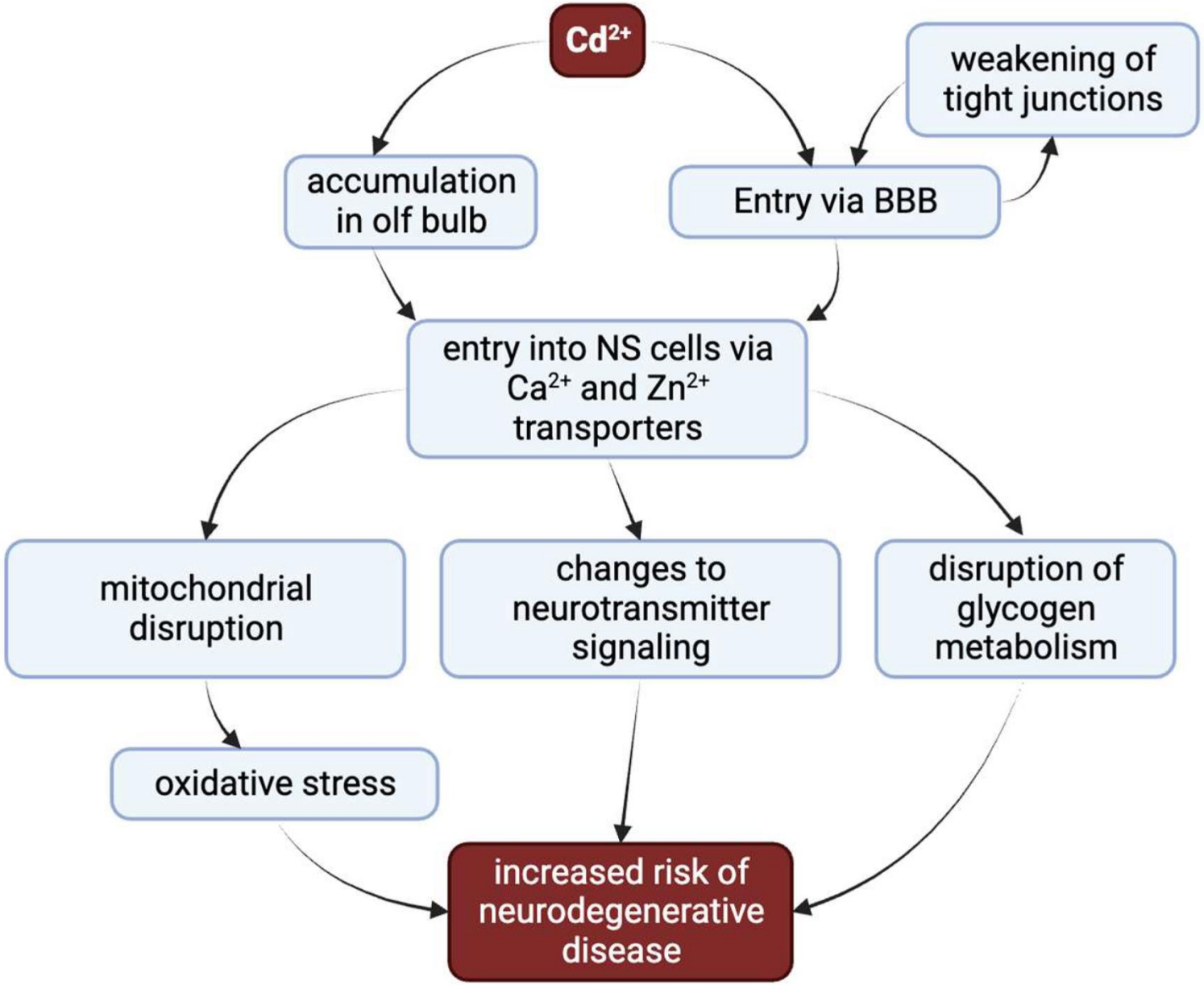


Int J Mol Sci. 2023 Nov 21;24(23):16558. doi: 10.3390/ijms242316558

Mechanisms of Cadmium Neurotoxicity

Madelyn A Arruebarrena [1], Calvin T Hawe [2], Young Min Lee [1], Rachel C Branco [1,2,*]

Cadmium is a heavy metal that increasingly contaminates food and drink products. Once ingested, cadmium exerts toxic effects that pose a significant threat to human health. The nervous system is particularly vulnerable to prolonged, low-dose cadmium exposure. This review article provides an overview of cadmium's primary mechanisms of neurotoxicity. Cadmium gains entry into the nervous system via zinc and calcium transporters, altering the homeostasis for these metal ions. Once within the nervous system, cadmium disrupts mitochondrial respiration by decreasing ATP synthesis and increasing the production of reactive oxygen species. Cadmium also impairs normal neurotransmission by increasing neurotransmitter release asynchronicity and disrupting neurotransmitter signaling proteins. Cadmium furthermore impairs the blood–brain barrier and alters the regulation of glycogen metabolism. Together, these mechanisms represent multiple sites of biochemical perturbation that result in cumulative nervous system damage which can increase the risk for neurological and neurodegenerative disorders. Understanding the way by which cadmium exerts its effects is critical for developing effective treatment and prevention strategies against cadmium-induced neurotoxic insult.



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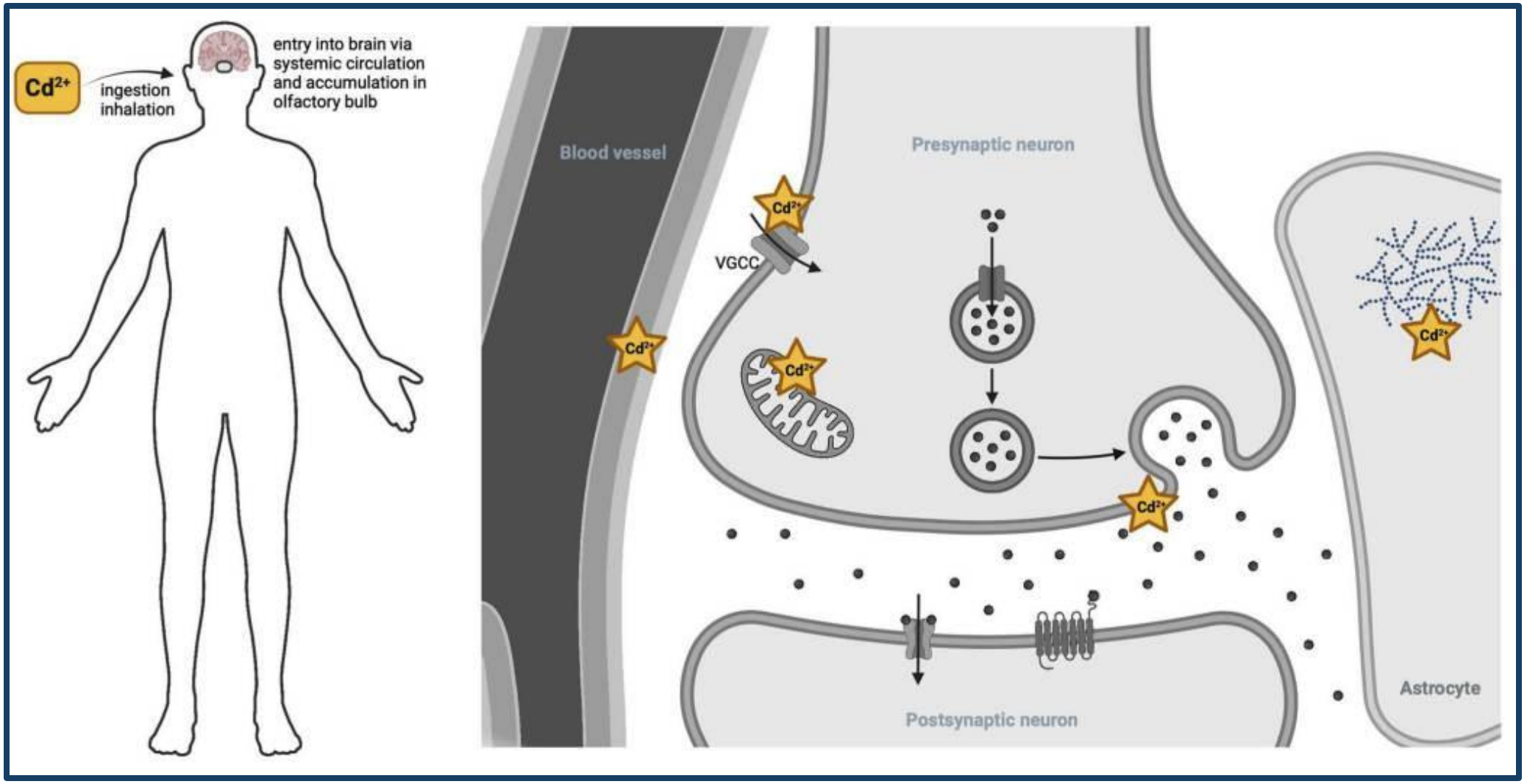

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Mechanisms of Cadmium Neurotoxicity

Cadmium has long been recognized as a potent inducer of oxidative stress, disrupting the balance between ROS and antioxidants within the nervous system, thereby posing a significant threat to neural health. The preceding sections of this review have illuminated the intricate web of mechanisms through which cadmium exerts its neurotoxic effects, from mitochondrial dysfunction to cholinergic neuronal loss. However, a promising avenue of research has emerged, shedding light on the potential protective measures that antioxidants offer against cadmium-induced neurotoxicity.

Thiol-containing proteins, including glutathione (GSH), bovine serum albumin (BSA), and selenoprotein P, have also emerged as key players in mitigating cadmium-induced neurotoxicity. These proteins, known for their capacity to scavenge free radicals and bind to cadmium, may act as a protective shield against the harmful effects of cadmium on neural tissues [36]. By decreasing the availability of free cadmium to bind to critical thiol groups on mitochondrial proteins, these antioxidants help maintain mitochondrial function and prevent cadmium-induced permeability transition pore (PTP) opening, ultimately preserving neuronal integrity.

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In a study utilizing Sprague–Dawley rats, cadmium exposure led to oxidative stress and autophagy within the testes. However, supplementation with the antioxidant quercetin demonstrated a protective ability to counteract Cd-induced testicular injury [142]. This finding highlights the potential of antioxidants to mitigate the adverse effects of cadmium on neural tissues. Furthermore, the neuroprotective potential of quercetin in the context of $CdCl_2$-induced hippocampal neurotoxicity in male rats revealed that quercetin exerted a beneficial impact by enhancing memory function and mitigating hippocampal damage in $CdCl_2$-treated rats. Quercetin increased the levels of antioxidants like glutathione (GSH) and manganese superoxide dismutase (MnSOD). Moreover, quercetin upregulated activity of SIRT1, a protein involved in cellular stress response, suppressed the activity of AChE, inhibited generation of ROS, and increased levels of brain-derived neurotrophic factor (BDNF), a protein crucial for neuronal survival and function [143].

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Editor: Athanasios Salifoglou

In terms of cadmium clearance, Ethylenediaminetetraacetic acid (EDTA) has shown promising results. EDTA serves as a chelating agent extensively employed for the purpose of sequestering divalent and trivalent metal ions. EDTA binds to the metals through four carboxylates and two amine groups and forms especially strong bonds with Mn (II), Cu (II), Fe (III), and Co (III) [145]. Due to this property, EDTA is utilized as a medical treatment for the removal of lead and cadmium to mitigate metal toxicity [146]. Studies such as Waters et al., 2001, have shown beneficial results in EDTA chelation therapy where significantly higher urinary losses of cadmium were observed [147]. Whereas these studies were focused on the loss of cadmium from the body, recent studies by Fulgenzi et al., 2020 have dived into the neurotoxicity aspect of such. EDTA in the use of toxic metal chelation therapy were shown to have beneficial effects on neurodegenerative diseases, showing promising results for the future on protective measures against cadmium [148].

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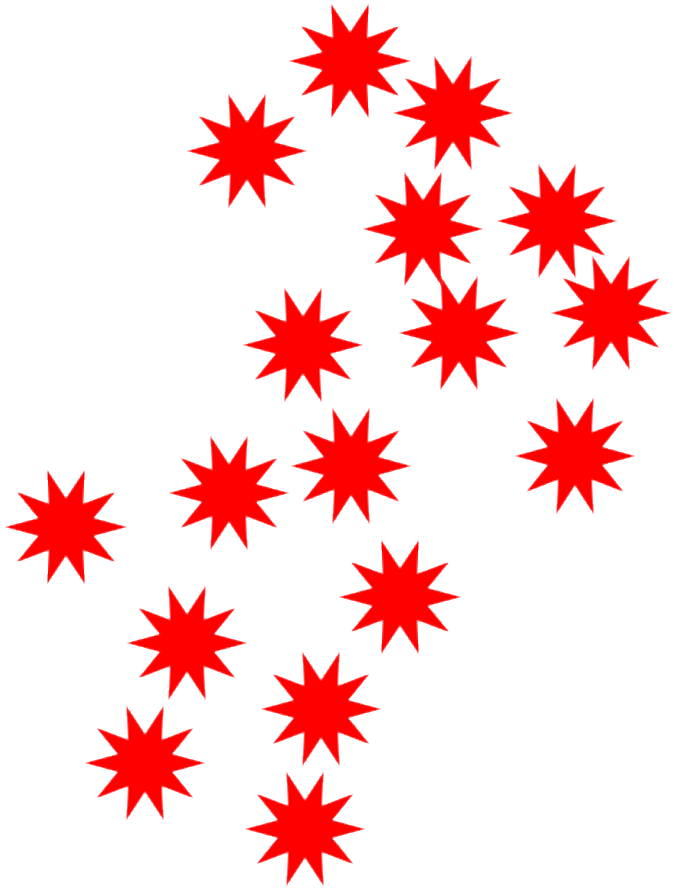
Zinc has also been suggested as a protective agent to counter cadmium neurotoxicity. Oral zinc supplementation is thought to prevent free radicals associated with cadmium-induced oxidative stress and alleviate cadmium-induced renal toxicity [151]. Oral supplementation has also been evidenced to slow the progression of neuronal senescence associated with cadmium toxicity and Alzheimer's disease by reducing Aβ plaque formation in mouse models [152]. However, zinc's protective functions with respect to neurotoxicity are much more complex and seem to be dose-dependent. Zinc supplementation at low doses protected rat hippocampal neurons from cadmium-induced disruption of neurotransmission but enhanced cadmium neurotoxicity at high doses [32]. More research is necessary to elucidate the intricate relationships between cadmium, zinc, Alzheimer's disease, and oxidative stress in efforts to develop zinc-based therapies for cadmium neurotoxicity.

= Glucose Molecule



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