REVIEW

Cadmium-induced neurotoxicity: still much ado

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Abstract

Cadmium (Cd) is a highly toxic heavy metal that accumulates in living system and as such is currently one of the most important occupational and environmental pollutants. Cd reaches into the environment by anthropogenic mobilization and it is absorbed from tobacco consumption or ingestion of contaminated substances. Its extremely long biological half-life (approximately 20–30 years in humans) and low rate of excretion from the body cause cadmium storage predominantly in soft tissues (primarily, liver and kidneys) with a diversity of toxic effects such as nephrotoxicity, hepatotoxicity, endocrine and reproductive toxicities. Moreover, a Cd-dependent neurotoxicity has been also related to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, and multiple sclerosis. At the cellular level, Cd affects cell proliferation, differentiation, apoptosis and other cellular activities. Among all these mechanisms, the Cd-dependent interference in DNA repair mechanisms as well as the generation of reactive oxygen species, seem to be the most important causes of its cellular toxicity. Nevertheless, there is still much to find out about its mechanisms of action and ways to reduce health risks. This article gives a brief review of the relevant mechanisms that it would be worth investigating in order to deep inside cadmium toxicity.

Key Words: *cadmium; toxicity; neurodegenerative disorders; oxidative stress; reactive oxygen species; blood-brain barrier permeability; metallothionein; 17β-estradiol; G-protein-coupled estrogen receptor-30*

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Cadmium (Cd) is the seventh most toxic heavy metal as per Agency for Toxic Substance and Disease Registry (ATDSR) ranking (Agency for Toxic Substance and Disease Registry, 2017) among the environmental pollutants, widely distributed in natural and industrial sources (reviewed in (Mead, 2010) with which humans and animals can potentially come in contact. Exposure to Cd can occur in occupations as the results of mining and ground water, commercial products, industrial effluents, industrial wastes, vehicle emissions, batteries, fertilizers, paints, and contaminated foods.

Cd can enter the human body by different mechanisms. Cd particles (Cd oxides or Cd dichloride) are transported along primary olfactory neurons and Cd accumulates in the olfactory bulb without further migration into the brain [reviewed in Sunderman (2001)]. Alternatively, after inhalation Cd accumulates into lungs and passing through the alveolar cells gets into the blood circulation [reviewed in Oberdörster (1992)]. Cd uptake by ingestion of Cd-containing food and/or water is the other major mechanism of Cd entry. At the apical membrane of enterocytes Cd is transported by the proton-metal cotransporter divalent metal transporter 1 (DMT1) (also DCT1, Nramp2, or *SLC11A2*). Cd export through the basolateral membrane is also mediated by transporters such as calcium-ATPases and zinc exporters [reviewed in Bridges and Zalups (2005)].

Following absorption by either lung or the intestinal epithelium, Cd enters the systemic circulation. Blood Cd concentration serves as a biomarker for Cd exposure level and some data indicated that blood Cd concentration in exposed individuals may range from just above 0 μM to 0.05 μM. Nonetheless, the blood Cd concentration of human varies remarkably according to age, gender, diet, residential area, and smoking status (Agency for Toxic Substance and Disease Registry, 2017). The effect of Cd exposure is strictly dose-dependent: at high doses Cd can progressively elicit cell injury, cell death, and organ failure, at low doses it may modulate specific mechanisms without marked cellular toxicity (López et al., 2003; Pacini et al., 2009).

From the outside of cells, Cd can alter the intracellular concentration of calcium which is a universal and versatile intracellular signal messenger (Berridge et al., 2000). Inside cells, Cd regulates Ca^{2+} signaling by exerting opposite effects on internal Ca^{2+} pools (**Figure 1a**). It blocks the release of stored Ca^{2+} by inhibiting the activity of 1,4,5-trisphosphate (IP_3) and ryanodine receptors. In contrast, it increases intracellular Ca^{2+} concentration by promoting calcium efflux from the sarcoplasmic reticulum [reviewed in Choong et al. (2014)].

Cd can penetrate into neurons *via* voltage-gated calcium channels (Usai et al., 1999). Indeed, a large body of *in vivo* and *in vitro* studies showed that exposure to Cd significantly affects the function of the peripheral (PNS) (Miura et al., 2013) and central nervous system (CNS) [reviewed in Marchetti (2014)] with a wide spectrum of clinical symptoms including olfactory dysfunction, peripheral neuropathy, neurological disturbances, mental retardation, and learning disabilities, as well as motor activity impairment and behavioral alterations both in adults and in children [reviewed in Wang and Du (2013)]. Moreover, Cd-dependent neurotoxicity as been also related to neurodegenerative diseases such as Alzheimer's

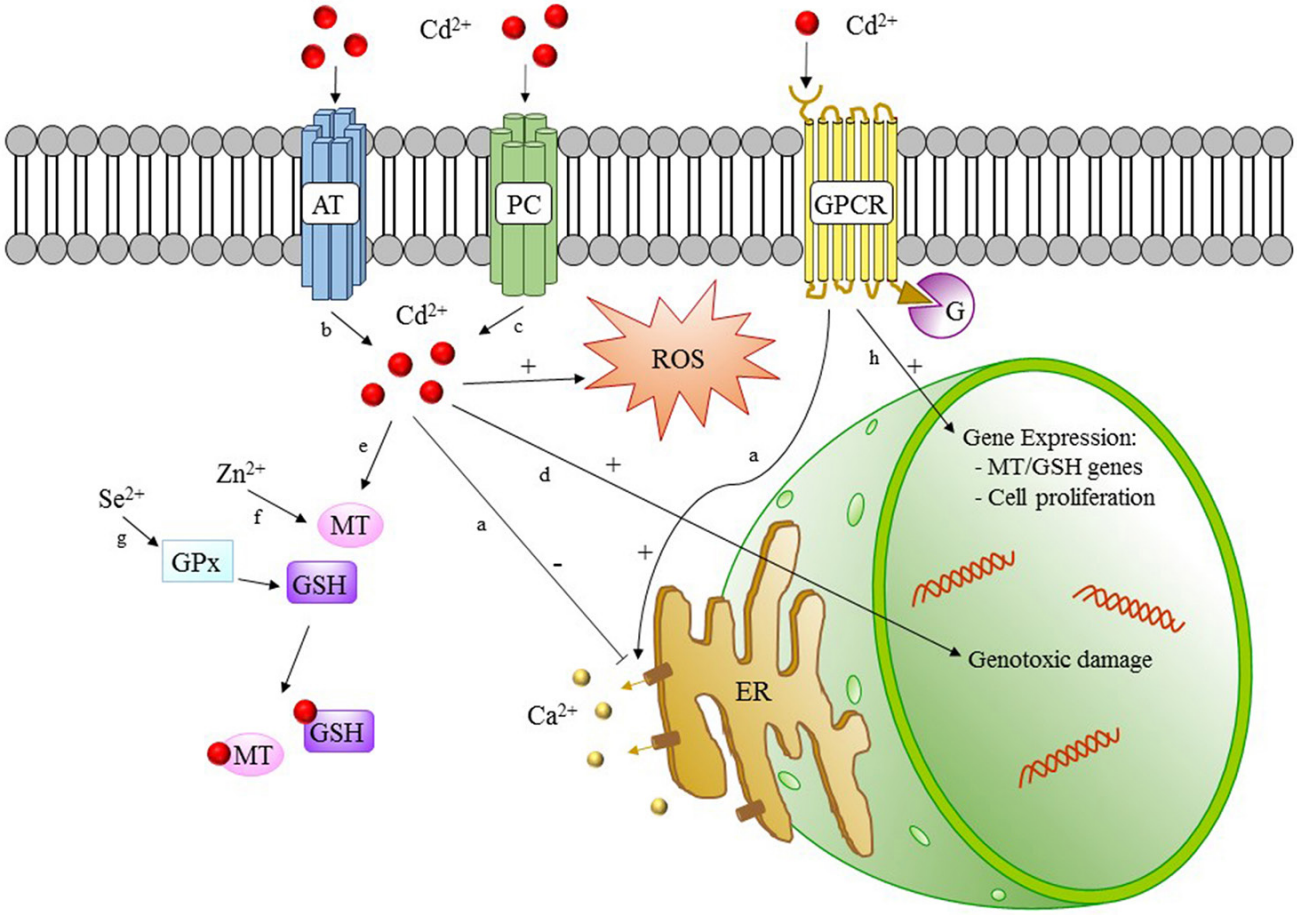

Figure 1 Schematic representation of selected cadmium (Cd)-related cellular pathways and nuclear interactions.
AT: Active ATPase transporter; PC: passive channel or carrier; GPCR: G-protein-coupled estrogen receptor-30 (GPR30); G: G-protein; MT: metallothionein; GSH: glutathione; GPx: Glutathione peroxidase; ROS: reactive oxygen species; ER: endoplasmic reticulum.

(AD) and Parkinson's diseases (PD) [reviewed in Chin-Chan et al. (2015)], as well as amyotrophic lateral sclerosis and multiple sclerosis [reviewed in Sheykhansari et al. (2018)], and myalgic encephalomyelitis (Pacini et al., 2012).

The uptake of Cd by mammalian cells occurs by both active (ATPase mediated efflux systems and receptor-mediated endocytosis) (**Figure 1b**) and passive (channels and carriers) transports (**Figure 1c**) [reviewed in Thévenod (2010)], and the similar chemical properties of Cd^{2+} and essential metals, especially Ca^{2+}, determine its entry [reviewed in Choong et al. (2014)]. Once inside the cell, the Cd-induced cytotoxicity differs from different organs [reviewed in Rani et al. (2014)], and depends on factors such as its different intracellular distribution (nuclear *vs*. cytoplasmic). The genotoxicity effect of Cd is known to affect the cell proliferation and differentiation, cell cycle progression, DNA synthesis, and apoptosis. Recently, an important Cd genomic effect is the inhibition of DNA repair [reviewed in Giaginis et al. (2006)] that represents a cause of genomic instability [reviewed in Hartwig et al. (2002)] leading to carcinogenesis, oxidative stress, proto-oncogene activation, altered DNA methylation and dysregulated gene expression [reviewed in Joseph (2009)] (**Figure 1d**).

On the other hand, the Cd cytotoxicity depends also on the induction of protective factors among which metallothionein activation, the stimulation of glutathione synthesis, and the presence of antioxidants. This latter feature, in particular, indicates the involvement of reactive oxygen species in the toxic response. Indeed, many reports indicate that the toxic mechanisms of Cd act intracellularly mainly *via* free-radical-induced production, particularly reactive oxygen species (ROS), which finally culminate into oxidative stress [reviewed in Jomova and Valko (2011)]. Many data regarding the modifications in thiol groups of antioxidant enzymes induced by oxidative stress are reported [extensively reviewed in Yang and Lee (2015)]. However, damage caused by low levels of oxidative stress can be neutralized by anti-oxidant enzymes. After exposure to low-dose Cd (1–10 μM), expression and activity of antioxidant enzymes including metallothionein (MT), catalase, glutathione S-transferase, glutathione peroxidase, and quinone oxidoreductase were substantially increased

as well as the glutathione (GSH) cellular levels [extensively reviewed in Sandbichler and Höckner (2016)]. On the other hand, since Cd has a high affinity to thiol groups, proteins containing thiol groups including MT and GSH are major carriers of Cd (**Figure 1e**).

Many studies have demonstrated that essential metals dietary supplements play important roles in protecting against Cd. Possessing similar chemical and physical properties to Cd, zinc (Zn) competes for binding sites of enzymatic proteins and induces the synthesis of the CNS specific metallothionein III that, in turn, binds to Cd causing its detoxification (**Figure 1f**). Moreover, Zn alleviates the Cd-dependent oxidative stress [reviewed in Matović et al. (2011)]. In addition to Zn, also selenium (Se) has been demonstrated to protect against Cd neurotoxicity. Indeed, as an important cofactor of the selenium glutathione peroxidase (GPx) enzyme (**Figure 1g**), on the one hand reduces oxidative stress, on the other enhances the cellular antioxidant capacity [reviewed in Nemmiche (2017)]. Despite the proven protective effects of Se against Cd neurotoxicity, it is important to highlight that the efficacy of Se strictly depends on the neuronal subtype. Recently, we have demonstrated that whereas Se is effective on catecholaminergic neurons, it is ineffective on cholinergic neurons (Branca et al., 2018). To this end, it is also important to stress that some subsets of cholinergic neurons express low levels of GPx (Trépanier et al., 1996); thus it is plausible to hypothesize that the lack of Se-mediated protection against Cd neurotoxicity in cholinergic neurons might be linked to their intrinsic GPx deficiency. The notion that the effects of Cd on the brain is region-specific (Kumar et al., 1996) would lend support to this hypothesis. To this regard, however, one of the key question that needs addressing is to understand the reason for the differential expression of the GPx enzyme in some subsets of cholinergic neurons (Trépanier et al., 1996).

Another interesting aspect that needs further investigation is the lack of ability of the Cd to penetrate the adult blood-brain barrier (BBB) and the blood-spinal fluid barrier, as well as the ependymal and pial surface. As a consequence young subjects that lack a fully operational BBB are more vulnerable to Cd (Antonio et al., 2002). However, even if many experimental studies have shown extensive histopathological damage in the cerebral and cerebellar cortices of growing animals compared to the adults, the mechanism concerning transport and metabolism of Cd in the brain is very poor. Furthermore, as mentioned above, Cd has been linked to the onset of several neurodegenerative diseases, such as AD, PD, and chronic traumatic encephalopathy characterized by alterations of the BBB (Shukla and Chandra, 1987; Shukla et al., 1987). This notion makes it plausible to hypothesize that Cd-mediated alterations of the BBB are at the basis of the degenerative disorders. This hypothesis is also supported by the observation of *in vivo* BBB dysfunction by exposure to Cd (Shukla et al., 1996).

To this end it would be important to dissect in details the molecular mechanism underlying Cd-dependent BBB alteration, and to determine whether the vascular endothelial cells lining the luminal surface of blood brain vessels are the primary potential target of circulating Cd, which might be important to explain the BBB alterations. This approach would help to ascertain whether BBB alterations could be primarily responsible for the effects of Cd on the CNS.

On the other hand, it would be important to address the role of the choroidal epithelia as the first line of defense against the detrimental effects of Cd on the CNS. The choroidal plexus, containing abundant metal binding ligands as well as high cystine concentration and significantly higher activities of superoxide dismutase and catalase, may effectively sequester Cd and prevent Cd entry into the CNS [reviewed in Zheng (2001)]. Thus, the need arises for a more comprehensive understanding of the molecular mechanisms that operate also in the choroid cells.

Another important aspect that has received little attention, is the estrogen-like effect of Cd. Cd is a well-known xenoestrogen that binds to estrogen receptor alpha and blocks the binding of 17β-estradiol in a noncompetitive manner. However, there is increasing evidence that G-protein-coupled estrogen receptor-30 (GPR30), a novel estrogen receptor, can mediate many estrogenic effects on the vasculature. GPR30 is a seven-transmembrane-spanning receptor that specifically binds to 17β-estradiol and causes rapid intracellular signaling. GPR30 has been linked to specific estrogen binding and rapid signaling [reviewed in Barton et al. (2018)]. Several groups have demonstrated GPR30 expression in the vascular endothelium of rodents and human cells evidencing an induction of actin polymerization and arrangement, as well as an inhibition of proliferation by the GPR30 selective agonist G-1 (Rowlands et al., 2011). Moreover, GPR30 has been demonstrated to mediate the proliferation of breast cancer cells induced by Cd (Yu et al., 2010). Nevertheless, the functional significance of this endothelial GPR30 is still largely unknown. A more extensive evaluation of GPR30 expression in barrier endothelial cells and the role of Cd in their stimulation and/or inhibition could open new scenarios in the understanding of the neurotoxic effects of Cd (**Figure 1h**).

The complexity of Cd-dependent neurotoxicity and its multiple effects in neural tissue points to its toxicity on brain homeostasis.

In conclusion, many aspects of the molecular mechanisms ensuing the entry of Cd into the cell remain to be clarified and more *in vivo* and *in vitro* studies are needed to thoroughly elucidate Cd-dependent relevant signaling cascades.

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