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Mini-review

Interplay of calcium and cadmium in mediating cadmium toxicity

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ABSTRACT

The environmentally important toxic metal, cadmium, exists as the Cd^{2+} ion in biological systems, and in this state structurally resembles Ca^{2+}. Thus, although cadmium exerts a broad range of adverse actions on cells by virtue of its propensity to bind to protein thiol groups, it is now well appreciated that Cd^{2+} participates in a number of Ca^{2+}-dependent pathways, attributable to its actions as a Ca^{2+} mimetic, with a central role for calmodulin, and the Ca^{2+}/calmodlin-dependent protein kinase II (CaMK-II) that mediates effects on cytoskeletal dynamics and apoptotic cell death. Cadmium interacts with receptors and ion channels on the cell surface, and with the intracellular estrogen receptor where it binds competitively to residues shared by Ca^{2+}. It increases cytosolic [Ca^{2+}] through several mechanisms, but also decreases transcript levels of some Ca^{2+}-transporter genes. It initiates mitochondrial apoptotic pathways, and activates calpains, contributing to mitochondria-independent apoptosis. However, the recent discovery of the role CaMK-II plays in Cd^{2+}-induced cell death, and subsequent implication of CaMK-II in Cd^{2+}-dependent alterations of cytoskeletal dynamics, has opened a new area of mechanistic cadmium toxicology that is a focus of this review. Calmodulin is necessary for induction of apoptosis by several agents, yet induction of apoptosis by Cd^{2+} is prevented by CaMK-II block, and Ca^{2+}-dependent phosphorylation of CaMK-II has been linked to increased Cd^{2+}-dependent apoptosis. Calmodulin antagonism suppresses Cd^{2+}-induced phosphorylation of Erk1/2 and the Akt survival pathway. The involvement of CaMK-II in the effects of Cd^{2+} on cell morphology, and particularly the actin cytoskeleton, is profound, favouring actin depolymerization, disrupting focal adhesions, and directing phosphorylated FAK into a cellular membrane. CaMK-II is also implicated in effects of Cd^{2+} on microtubules and cadherin junctions. A key question for future cadmium research is whether cytoskeletal disruption leads to apoptosis, or rather if apoptosis initiates cytoskeletal disruption in the context of Cd^{2+}.

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Abbreviations: AIF, apoptosis-inducing factor; CaM, calmodulin; CaMK-II, Ca^{2+}/calmodulin-dependent protein kinase II; CaMP, Ca^{2+}/CaM-dependent protein kinases phosphatase; ERα, estrogen receptor α; Erk, extracellular signal-regulated kinase; FA, focal adhesion; FAK, focal adhesion kinase; IP_3, inositol trisphosphate; JNK, cJun N-terminal kinase; MAP, microtubule associated protein; MAPK, mitogen activated protein kinase; MT, microtuble; MTPT, mitochondrial permeability transition pore; NOS, nitric oxide synthetase; PDE, phosphodiesterase; PLC, phospholipase C; PMCA, plasma membrane Ca^{2+}-ATPase; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SOC, store-operated Ca^{2+} channel; SR, sarcoplasmic reticulum; TFP, trifluoperzaine; TPEN, tetrakis-(2-pyridylmethyl)ethylenediamine; TRP, transient receptor protein; VDDC, voltage-dependent calcium channel.

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1. Introduction

Cadmium (Cd) is a toxic metal occurring in the environment that has been shown to cause adverse health effects in the general population [1–4], and is listed as a class I carcinogen by the International Agency for Research on Cancer [5]. Major sources of Cd exposure in an occupational setting occur in industries involved with Cd and Zn mining and refining, electroplating, and battery, plastics, pigment, electronics production [6,7]. Such occupational exposures are now generally minimized by careful practices of industrial hygiene, as well as by regulation of usage. Historically, Germany and the Scandinavian countries were among the first jurisdictions to attempt to control environmental exposure by selectively banning use of Cd in some forms. Now, severe restrictions are being implemented throughout the European Union under the Registration, Evaluation, Authorization and Restrictions of chemicals (REACH) program, and a decline in use of Cd in coatings, pigments and stabilizers has meant that currently the major consumption of Cd is in the production of Ni–Cd batteries.

Because Cd is not degraded, its continual release into the environment from industrial activity results in an ever-increasing environmental burden and entry into the food chain [6]. In recent years, then, attention has shifted from the obvious effects of Cd in occupational health to recognition of Cd as an important environmental problem. Non-occupational exposure is mainly from the diet [3], with an estimated individual daily consumption of 30 μg in the USA, and considerably higher in China and Japan [8]. Because of the Cd content of tobacco, smokers have several times the blood levels and kidney concentrations of Cd found in non-smokers. Epidemiological studies such as Cadmibel [9,10] have drawn attention to exposure in the general population, and widespread toxicity among wildlife is recognized [11]. Evidence is mounting that environmental exposures are associated with cancers of the kidney, bladder, prostate, and endometrium [1]. Studies from the Karolinska Institute have identified a benchmark dose for Cd that produces a definite renal response in Swedish and Japanese populations with low environmental exposure [12], and have concluded that there is no margin of safety between the onset of adverse effects on the kidney and Cd exposures in the general population [1]. A recent review of Cd exposure from different food sources notes that speciation (i.e., Cd^{2+} vs. protein-bound Cd) does not play a significant role in Cd bioavailability [13]. Nordberg [14] has provided a historical review on the development of Cd toxicology.

Newer sources of Cd exposure are worth mentioning as these raise a cautionary note for future risk and global health impact. Unregulated recycling of e-waste as a cottage industry is exposing children and adults to extreme levels of Cd in Asia and Africa [15,16]. Phosphate-based fertilizers containing natural amounts of Cd have recently been termed the "Trojan Horse of the green revolution" as outbreaks of endemic chronic renal failure appeared in Sri Lanka following increased Cd contamination of soil and water from increased fertilization [17]; such cases should be anticipated elsewhere in developing countries. Quantum dots based on CdSe and CdTe are being developed for possible medical applications, and their toxicity is largely unknown [18,19]. And, a growing use of Cd in the manufacture of CdTe solar panels is exempt from some regulations.

Of major concern is that Cd has a long biological half-life (10–30 years in humans) in part due to its low excretion rate and ability to accumulate in various tissues [1,20]. Depending on the dose, route, and duration of exposure, the major organ systems affected by Cd include the lungs, liver, kidney, and muscoskeletal system [1,14]. In particular, the liver and the kidney generally contain a third of the total Cd load in the body. Prolonged exposure to Cd can lead to renal dysfunction and osteomalacia in humans. Nephrotoxic damage is considered to be an underlying factor for establishing important biomarkers of Cd toxicity, resulting as it does in proteinuria, polyuria, and general dysfunction of the kidney.

Cadmium is not a physiologically necessary metal, and it can disrupt signaling cascades that lead to a variety of toxic effects. In particular, because of the physicochemical similarities between Cd^{2+} and calcium ion (Ca^{2+}), many studies have sought to determine how Cd can effect changes in calcium signaling pathways and their resultant toxic effects. This review will focus on changes in intracellular cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_i$), and the role of calcium effectors, calmodulin (CaM) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMK-II) in mediating cadmium toxicity.

2. Physicochemical properties of cadmium and calcium

Cadmium is a group 12 element in the periodic table with a complete 4*d* electron shell, resulting in a very stable divalent cation (Cd^{2+}). Calcium ion (Ca^{2+}) is found in the group 2 elements, and also occurs as a divalent cation in aqueous solution. Divalent Cd^{2+} and Ca^{2+} have very similar physicochemical properties, with ionic radii of Ca^{2+} (0.97 Å) and Cd^{2+} (0.99 Å) giving similar charge/radius ratios (Ca^{2+} = 2.02 e/Å, Cd^{2+} = 2.06 e/Å), determining that these ions are able to exert strong electrostatic forces on biological macromolecules [21]. This favours the exchange of the two metals in Ca^{2+}-binding proteins, and it has been shown that Cd^{2+} can displace Ca^{2+} from its binding sites in calmodulin (CaM) [22], sarcolemma [23], and troponin C [24] *in vitro*, with the potential to affect other Ca^{2+}-binding proteins.

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