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Review

Pro-inflammatory properties of cadmium

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Cadmium is a toxic and carcinogenic heavy metal that nowadays constitutes a serious environmental health problem. The aim of this study is to review the effects of cadmium on selected inflammatory mediators and markers, such as NF-κB and AP-1 transcription factors, IL-6, TNF-α, IL-1β cytokines, IL-8 or MIP-2 chemokine, MPO, iNOS, MMPs and COX-2 enzymes, PGE_2 (product of COX-2 enzyme), ICAM-1, VCAM-1 and PECAM-1 adhesion molecules, and CRP. The research strategy identified articles available in Medline, published between 1998 and 2012; we included both *in vivo* and *in vitro* studies carried out on humans and rodents. Most of the reviewed research findings suggest that cadmium in micromolar concentrations (especially in the 1–10 μM range) causes up-regulation of the mediators and markers of inflammation, and appears to have pro-inflammatory properties. However, it is worth mentioning that a contradictory or even opposite hypothesis exists, which suggests cadmium to be an anti-inflammatory factor. Further research including detailed histological analyses should solve this discrepancy. Nevertheless, it appears that the main reason for these contradictory findings is the experimental setup: different biological systems analyzed and different doses of cadmium applied.

Key words: cadmium, inflammatory mediators and markers

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INTRODUCTION

Cadmium is a heavy metal that nowadays constitutes a serious environmental hazard for human health (Jarup, 2002; Godt *et al*., 2006; Jarup & Akesson, 2009). The most significant sources of occupational cadmium exposure include: the nickel-cadmium battery industry, fume inhalation, electroplating and paint pigments (Klassen *et al*., 2009). The major source of cadmium exposure for the general population is food; in addition, cigarette smoking is another important contributor to the cadmium body burden (Klassen *et al*., 2009). The other, minor sources of exposure to that metal are: inhalation of ambient air, ingestion of drinking water, contaminated soil or dust (IARC, 2012). There are three possible routes of cadmium absorption: gastrointestinal, respiratory and dermal (Godt *et al*., 2006). Concentration of cadmium in blood is a good biomarker for both recent and cumulative exposure to this metal. Among the general population, normal cadmium blood levels are in the range of 3.5–8.9 nM for non-smokers and 12.4–35.5 nM for smokers; however, much higher levels have been reported for environmental exposure (above 89 nM) and occupational exposure (up to 445 nM) (IARC, 2012). Cadmium was found to exert its toxicity in many organs, such as kidneys, liver, lungs, pancreas, testes, placenta, brain and bones (Cuypers *et al*., 2010). The mechanisms of toxic action of cadmium in cells include: decrease in anti-oxidant potential, decrease in thiol status, activation of signaling pathways, inhibition of DNA methylation and DNA repair, and cell damage (Czeczot & Skrzycki, 2010). Metallothioneins, small, cysteine-rich, metal-binding proteins, were reported to play a protective role against cadmium toxicity. (Klassen *et al*., 2009). Cadmium is also considered to have carcinogenic properties – the International Agency of Research on Cancer classified this metal and its compounds as Group 1 human carcinogens (IARC, 2012).

Inflammation is a complicated and complex process. It is a protective response of organism to injury (caused by physical stimuli, chemical agents, etc.) or infection (caused by microorganisms), whose role is to eliminate injury-inducing agents, prevent tissue damage and/or initiate repair processes and restore physiological functions of the tissue or organ affected by the inflammatory process (Das, 2011). The essential components of the inflammatory reaction are the vascular and cellular responses. Inflammation, either acute or chronic, is mediated by a number of chemical factors (proteins, lipids, lipoproteins) secreted by cells participating in the inflammatory process either directly and/or responding to the inflammatory stimulus (Das, 2011). The action of these chemical mediators (single, combined or sequential) leads to the amplification of the tissues/organs' response to the stimulus and affects the course of inflammation. In addition, the chemicals liberated from cells or tissues undergoing necrosis or apoptosis during the inflammation/repair have also the ability to take part in the inflammatory process itself (Das, 2011).

A number of review articles dealing with cadmium toxicity can be found (Martynowicz & Skoczyńska, 2003;

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Abbreviations: AP-1, activator protein-1; A549, human lung adenocarcinoma cell line; BALF, bronchoalveolar lavage fluid; BNL CL.2, murine embryonic liver cells; COX-2, cyclooxygenase-2; CRP, C-reactive protein; Calu-3, human bronchial epithelial cell line; HepG2, human liver carcinoma cell line; ICAM-1, Intercellular adhesion molecule-1; IL-6, interleukin-6; IL-1β, interleukin-1β; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; MIP-2, macrophage inflammatory protein-2; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; NF-κB, nuclear factor κB; PECAM-1, Platelet-endothelial adhesion molecule-1; PGE_2, prostaglandin E_2; PBMCs, peripheral blood mononuclear cells; SAEC, small airway epithelial cells; TIMPs, tissue inhibitors of metalloproteinases; THP-1, human acute monocytic leukemia cell line; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1.

Mlynek & Skoczyńska, 2005; Valko *et al*., 2005; Bertin & Averbeck, 2006; Prozialeck *et al*., 2006; Fowler, 2009; Jarup & Akesson, 2009; Klassen *et al*., 2009; Czeczot & Skrzycki, 2010). However, to our best knowledge, there was no single review paper focusing solely on the pro-inflammatory properties of cadmium that would present the updated research findings on that topic. Therefore, the aim of this study is to review the effects of cadmium on selected inflammatory mediators and markers, such as NF-κB and AP-1 transcription factors, IL-6, TNF-α, IL-1β cytokines, IL-8 or MIP-2 chemokine, MPO, iNOS, MMPs and COX-2 enzymes, PGE_2 (product of COX-2 enzyme), ICAM-1, VCAM-1 and PECAM-1 adhesion molecules, and CRP. The research strategy identified articles available in Medline, published between 1998 and 2012; we included both *in vivo* and *in vitro* studies carried out on humans and rodents.

CADMIUM AND NF-κB

NF-κB is an inducible and ubiquitously expressed transcription factor for genes involved in different processes like cell survival, differentiation, inflammation and growth (Valko *et al*., 2005). This family of transcription factors is central to induction of inflammation (Valko *et al*., 2005). Different external stimuli can activate NF-κB, including carcinogens and tumor promoters, such as toxic metals, UV radiation, phorbol esters, asbestos and alcohol (Valko *et al*., 2005). Acute cadmium exposure was shown to activate NF-κB in various systems. Hart and coworkers used rat lung epithelial cells to study the effects of cadmium (in low micromolar concentrations) on apoptosis and found that this process induction by Cd was associated with the activation of NF-κB (Hart *et al*., 1999). Yang and coworkers analyzed rat primary microglia-enriched cultures and demonstrated that cadmium treatment (0.625 μM and 2.5 μM for 6 hours) dramatically increased NF-κB binding to the DNA (Yang *et al*., 2007). Freitas and Fernandez demonstrated stimulatory effect of cadmium in higher concentrations (>10 μM) on the activation of NF-κB by human THP-1 cells (Freitas & Fernandes, 2011). Go *et al*. (2012) used both *in vitro* (HeLa cells) and *in vivo* (transgenic mouse line) models and showed that low-dose exposure to cadmium increased the activity of NF-κB. Also, the results of an *in vivo* study, carried out on mice treated with cadmium chloride ($CdCl_2$) showed that cadmium caused significant increase in the expression of NF-κB (Lee & Lim, 2011). However, one study was at variance; the authors concluded that the activation of NF-κB was not increased after Cd treatment (1.5 or 10 μM $CdCl_2$) of HepG2 cells derived from a human liver hepatoma (Souza *et al*., 2004).

CADMIUM AND AP-1

Activator protein-1 (AP-1) transcription factors, transcription regulators of a variety of genes, is a collection of proteins belonging to the Jun, Fos, MAF and ATF subfamilies that can bind the tumor-promoting agent (TPA) or cAMP response elements (Valko *et al*., 2005; Lee & Lim, 2011). AP-1 in nucleus is influenced by the cellular redox status and was implicated as playing important roles in pro-inflammatory and carcinogenic events (Lee & Lim, 2011; Lee & Lim, 2011). AP-1 was reported to regulate expressions of COX-2 and iNOS pro-inflammatory factors (Lee & Lim, 2011). Souza and coworkers demonstrated that treatment of HepG2 cells with $CdCl_2$ at concentrations of 1, 3, 5, 10 or 20 μM for 4 hours significantly increased AP-1 activation as compared to control cells (Souza *et al*., 2004). Bertin and Averbeck showed in their review article that cadmium induced overexpression of c-Fos and c-Jun transcription factors (Bertin & Averbeck, 2006). Another group of researchers (Yang and coworkers) used rat primary neuron-glia cultures to examine cadmium-induced neurotoxicity (Yang et al., 2007). Cadmium treatment (0.625 μM and 2.5 μM) was demonstrated to cause a dramatic increase in the activation of AP-1 six hours post-treatment (Yang et al., 2007). One of the recent studies by Lee and Lim was conducted using BNL CL.2 cells (murine embryonic liver cells); the authors showed a significant increase in the activation of c-Jun and c-Fos transcription factors in these cells, 24 hours after exposure to 10 μM $CdCl_2$ (Lee & Lim, 2011). Also, an *in vivo* study carried out on mice revealed that treatment with 2.5 mg/kg $CdCl_2$ significantly increased the expression level of AP-1 in liver tissues (Lee & Lim, 2011).

CADMIUM AND IL-6

Interleukin-6 (IL-6), a very important pro-inflammatory cytokine, known as a traditional marker of inflammation, promotes the induction of acute phase proteins, but may also be involved in regulation of the transition from acute to chronic inflammation and stimulation of T- and B-lymphocytes (Lag *et al*., 2010). Souza analyzed IL-6 gene expression of HepG2 cells treated with $CdCl_2$ (1, 5, 10 μM) for 1, 3 or 6 hours. Statistically significant increase in IL-6 mRNA was detected with 5 and 10 μM $CdCl_2$ only after a 3-hour treatment (Souza *et al*., 2004). In another study, interleukin-6 cell production was measured in cultures of lung cells of rats treated with cadmium (Kataranovski *et al*., 2009). The authors demonstrated increased spontaneous IL-6 production in cultures of cells from cadmium treated rats (0.5 and 1 mg Cd/kg b.w.) (Kataranovski *et al*., 2009). Lag and coworkers examined cadmium effects on different cellular systems relevant for lung toxicity: human M1 fibroblast cultures and rat primary lung cell cultures, i.e. type 2 cell-enriched cultures and alveolar macrophages (Lag *et al*., 2010). Cadmium was shown to significantly increase the expression level of IL-6 during the exposure of human M1 fibroblasts to 7 μM Cd^{2+} for 7 hours. Similarly, in type 2 cell-enriched cultures the mRNA levels of IL-6 were also increased during the exposure to 3 μM of cadmium for 2-20 hours, compared to control, however in alveolar macrophages the mRNA levels of IL-6 were unaltered during such exposure (Lag *et al*., 2010). Cadmium induced a significant increase in the release of IL-6 from both M1 fibroblasts and type 2 epithelial cell-enriched cultures, but not from alveolar macrophages (Lag *et al*., 2010). Similarly, Rennolds and coworkers showed in their study that cadmium (50 μM $CdSO_4$ for 24 hours) increased the secretion of IL-6 by human bronchial epithelial cell line Calu-3 (Rennolds *et al*., 2012). These results were replicated by Cormet-Boyaka and coworkers, who also demonstrated that cadmium treatment (2 and 5 μM Cd for 24 hours) induced the secretion of IL-6 by primary human small airway epithelial cells (SAEC) (Cormet-Boyaka *et al*., 2012). Kundu and coworkers in an *in vitro* study carried out on human lung adenocarcinoma cell line (A549) found the up-regulation of IL-6 in cadmium-treated cells (2.5 μM at 24 hours) (Kundu *et al*., 2011). Freitas and Fernandes demonstrated that cadmium induced the release of IL-6 in THP-1 mono-

cytic cells (Freitas & Fernandes, 2011). In line with previous studies are the results of the *in vivo* study of Lee and Lim, who showed that treatment of ICR mice with $CdCl_2$ (2.5 mg/kg b.w.) resulted in significant increase in the expression of IL-6 in mouse liver tissue (Lee & Lim, 2011). Kundu and coworkers showed that prolonged exposure of Swiss albino mice to low concentration of cadmium (5 mg/kg b.w.) caused significant increase in the expression of IL-6 in lung cells (Kundu *et al.*, 2009). Also, the study of Yazihan *et al.* demonstrated that chronic administration of cadmium (15 ppm Cd for 8 weeks) to Wistar rats resulted in significant increase in IL-6 level in heart tissue supernatants as compared to controls (325 *vs* 150 pg/g tissue) (Yazihan *et al.*, 2011). Afolabi *et al.* administered 50 and 100 ppm cadmium to rats through drinking water for 7 weeks and found 87% and 57% increase in plasma IL-6 levels, respectively (Afolabi *et al.*, 2012). Stosic and coworkers revealed gender differences in cytokine levels in lung homogenates of rats following intraperitoneal administration of cadmium (1 mg/kg b.w.) — higher content of IL-6 detected in lungs of female rats (Stosic *et al.*, 2010).

CADMIUM AND TNF-α

Tumor-necrosis factor (TNF), a cytokine produced by activated macrophages in response to pathogens and other injurious stimuli, is a necessary and sufficient mediator of local and systemic inflammation (Tracey, 2002). TNF-α amplifies and prolongs the inflammatory response by activating other cells to release both cytokines such as IL-1, and mediators such as eicosanoids, nitric oxide and reactive oxygen species, which promote further inflammation and tissue injury (Tracey, 2002). The review of literature suggests differential effects of cadmium exposure on TNF-α production and gene expression, depending on biological system analyzed (Dong *et al.*, 1998; Souza *et al.*, 2004; Zhao *et al.*, 2006; Lag *et al.*, 2010; Stosic *et al.*, 2010; Freitas & Fernandes, 2011; Kundu *et al.*, 2011; Lee & Lim, 2011; Yazihan *et al.*, 2011; Afolabi *et al.*, 2012; Cormet-Boyaka *et al.*, 2012). Dong and coworkers treated human HepG2 cells with 1, 10 and 100 μM $CdCl_2$ for 18 hours and found that gene expression and secretion of TNF-α were increased, however relatively high concentrations of $CdCl_2$ were needed to stimulate TNF-α secretion (Dong *et al.*, 1998). Souza *et al.* incubated HepG2 cells with 1, 5 or 10 μM $CdCl_2$ for 0.5, 1, 3 or 6 hours and showed an increase in TNF-α gene expression: the maximum increase in TNF-α gene expression was observed after 1 hour of cadmium treatment (Souza *et al.*, 2004). Lag *et al.* demonstrated that cadmium seemed to induce a concentration dependent change (from 3 to 10 μM) in the TNF-α release by rat alveolar macrophages after exposure for 20 hours, with the highest increase for 10 μM Cd^{2+} (Lag *et al.*, 2010). Haase and coworkers examined the effect of a 24-hour exposure to $CdSO_4$ (1.25 and 10 μM) on TNF-α production in murine Raw 264.7 macrophages. The authors observed a dose-response relationship between Cd concentration and TNF-α production (Haase *et al.*, 2010). Freitas and Fernandez demonstrated in their study that cadmium exposure induced the release of TNF-α in THP-1 human monocytic leukemia cell line (Freitas & Fernandes, 2011). Kundu *et al.* examined the effects of cadmium on inflammatory response in transformed human lung adenocarcinoma epithelial cell line (A549), and found that $CdCl_2$ (2.5 μM) up-regulated the expression of TNF-α at both 24 and 48 hours (Kundu *et al.*, 2011). However, in one of the recent studies, Cormet-Boyaka and coworkers demonstrated that cadmium treatment did not induce the secretion of TNF-α both by primary human SAEC and Calu-3 cells (Cormet-Boyaka *et al.*, 2012). The results of Lag and coworkers show that in type 2 cell-enriched rat primary lung cell cultures the mRNA levels of TNF-α were reduced after exposure to 3 μM Cd for 2-20 hours, whereas the mRNA levels of TNF-α were unaltered or reduced during the exposure of alveolar macrophages to 3 μM Cd for 2-20 hours. The TNF-α release from type 2-enriched cells was not changed after 20 hours of exposure to different concentrations of cadmium (1, 3, 6 and 10 μM) (Lag *et al.*, 2010).

Zhao and coworkers investigated acute inflammatory response in the intestines of mice following $CdCl_2$ oral exposure (Zhao *et al.*, 2006). The authors found that both in mice orally challenged with 25 mg/kg b.w. of $CdCl_2$ and those with 100 mg/kg b.w. of $CdCl_2$, the expression of TNF-α mRNA in duodenum and jejunum did not change significantly from the control group from 0 to 24 hours after cadmium administration (Zhao *et al.*, 2006). However, other group of researchers showed that $CdCl_2$ treatment (2.5 mg/kg b.w.) of ICR mice significantly increased the expression level of TNF-α mRNA in liver tissue as compared to control (Lee & Lim, 2011). Yazihan *et al.* demonstrated that chronic exposure of Wistar rats to 15 ppm Cd caused a marked increase in TNF-α level in heart tissue (Cd: 793 pg/g tissue, control: 402 pg/g tissue) (Yazihan *et al.*, 2011). In a study of Afolabi *et al.*, a 7-week exposure of rats to 50 and 100 ppm cadmium through drinking water resulted in 336% and 470% increase in TNF-α plasma levels, respectively, as compared to controls (Afolabi *et al.*, 2012). Stosic *et al.* demonstrated that intraperitoneal administration of cadmium (1 mg/kg b.w.) to rats caused a higher TNF-α content in lung homogenates of males than females (Stosic *et al.*, 2010).

CADMIUM AND IL-1β

IL-1β, together with TNF-α, plays an important role in the onset of inflammatory processes that regulate the expression of other cytokines and chemokines (Lag *et al.*, 2010). Lag and coworkers found that the pattern of IL-1β expression and cytokine release was the same as for TNF-α; exposure to 3 μM Cd^{2+} for 2-20 hours resulted in the reduction of mRNA levels of IL-1β in type 2 cell-enriched rat primary lung cell cultures, and no change or reduction of mRNA level of IL-1β in alveolar macrophages. IL-1β release from type 2 cell-enriched cells and level was not affected by cadmium treatment (Lag *et al.*, 2010). The study of Cormet-Boyaka *et al.* showed no effect of cadmium on IL-1β secretion by both primary human SAEC and Calu-3 cells (Cormet-Boyaka *et al.*, 2012).

However, rat alveolar macrophages were reported to release IL-1β with a concentration-dependent increase, with 6 μM Cd^{2+} inducing the highest increase (Lag *et al.*, 2010). Souza demonstrated that cadmium induced the increase in IL-1β gene expression in HepG2 cells; the maximum increase was noted after 1 hour of treatment (Souza *et al.*, 2004). The results of an *in vivo* study of Zhao *et al.* (2006) showed that $CdCl_2$ administered orally to mice did not change the expression of IL-1β in duodenum and jejunum.

CADMIUM AND IL-8

Interleukin-8 (and its mouse homolog MIP-2) is a chemokine that plays a pivotal role in different human organs by recruiting neutrophils and macrophages to the site of inflammation (Cormet-Boyaka *et al.*, 2012). Using human HepG2 cells and freshly isolated mouse hepatocytes, Dong demonstrated that cadmium (1, 10 and 100 μM $CdCl_2$) increased gene expression and secretion of IL-8 (by human HepG2) or MIP-2 (by mouse hepatocytes) in a dose-dependent manner (Dong *et al.*, 1998). Another group of researchers also showed that cadmium treatment (1.5 or 10 μM $CdCl_2$) of HepG2 cells for 0.5–6 hours resulted in the increase in IL-8 gene expression, with a maximum effect achieved after 3 hours of cadmium incubation (Souza *et al.*, 2004).

Lag and coworkers found that IL-8 release from M1 human fibroblasts was significantly increased after cadmium treatment (6–10 μM Cd^{2+}) for 20 hours (Lag *et al.*, 2010). In type 2 cell-enriched rat primary lung cell cultures, the MIP-2 mRNA levels were increased during the exposure to 3 μM Cd for 2-20 hours; also the MIP-2 release showed concentration-dependent increase with a maximal response at 6–10 μM cadmium exposure (Lag *et al.*, 2010). However, in rat alveolar macrophages the mRNA levels of MIP-2 were unaltered during the exposure to 3 μM Cd^{2+} for 2–20 hours. The MIP-2 release from alveolar macrophages was significantly increased only at the highest applied cadmium concentration – 10 μM (Lag *et al.*, 2010). Zhao *et al.* showed that $CdCl_2$ significantly increased the expression of MIP-2 mRNA in duodenal and proximal jejunal tissue of mice 3 hours after the application of a single oral dose of $CdCl_2$ (Zhao *et al.*, 2006). That increase appeared to be dose-dependent over a dosage range of 25-100 mg/kg b.w.

Rennolds and coworkers investigated the effects of a 24-hour cadmium treatment (5 and 50 μM) on IL-8 secretion by human bronchial epithelial (HBE) cells, and found that this metal induced IL-8 secretion into the apical compartment in a dose-dependent manner (Rennolds *et al.*, 2012). Also the IL-8 mRNA level was significantly increased during 4 hours of exposure of HBE cells to 50 μM cadmium (Rennolds *et al.*, 2012). In another study, primary human SAEC were exposed to 2 and 5 μM cadmium for 24 hours and appeared to secrete IL-8 in a dose-dependent manner (Cormet-Boyaka *et al*, 2012); the IL-8 mRNA levels were also increased in SAEC treated with 2-5 μM cadmium for 4 hours (3-fold increase with 5 μM Cd) (Cormet-Boyaka *et al*, 2012). In that study, another cell line, human airway epithelial Calu-3 cells were incubated for 24 hours with 2-50 μM cadmium. The authors demonstrated that stimulation of IL-8 secretion by cadmium was a dose-dependent process. The release of IL-8 by Calu-3 cells was also time-dependent: the cells treated with 50 μM Cd appeared to increase the IL-8 release with the increasing exposure time from 2 to 6 hours. The release of IL-8 was associated with an increase in IL-8 mRNA levels during a 4-hour cadmium incubation (Cormet-Boyaka *et al*, 2012). Another experiment revealed the dose-dependent (2-50 μM Cd) induction of IL-8 mRNA levels by cadmium (Cormet-Boyaka *et al*, 2012). Freitas and Fernandes demonstrated in their study that cadmium significantly induced the release of IL-8 chemokine from human THP-1 monocytic cells (Freitas & Fernandes, 2011).

CADMIUM AND INFLAMMATORY CELLS RECRUITMENT

Myeloperoxidase (MPO) is an enzyme, mainly released by activated neutrophils (but also macrophages) that possesses the powerful pro-oxidative and pro-inflammatory properties (Kataranovski *et al.*, 2009). This enzyme activity is a measure of inflammatory cells infiltration (Zhao *et al.*, 2006). Kataranovski and coworkers investigated the effects of systemic cadmium administration (0.5 mg/kg and 1 mg/kg b.w.) on pulmonary inflammation in rats (Kataranovski *et al.*, 2009). MPO content in lungs corroborated neutrophil infiltration: significantly elevated MPO activity in lung homogenates was found, following administration of 0.5 mg Cd/kg b.w., while the highest increase was demonstrated at a higher cadmium dose applied (Kataranovski *et al.*, 2009). Stosic *et al* used a similar experimental model; the authors found that intraperitoneal administration of cadmium (1 mg/kg) to rats resulted in an increased MPO content in lung cells of both sexes of cadmium-treated animals, however, a higher MPO content was noted in males (Stosic *et al.*, 2010). Zhao *et al.* measured MPO activity in duodenum and found that $CdCl_2$ in concentration of 100 mg/kg b.w., administered orally to mice induced the significant increase in MPO activity, 24 hours after the challenge. This increase was dose-dependent with dosages of 50 and 100 mg Cd/kg b.w. inducing a significant elevation of tissue MPO activity (Zhao *et al.*, 2006).

CADMIUM AND ADHESION MOLECULES

Cell surface adhesion molecules were found to be essential components in inflammation and immune surveillance processes (Seok *et al.*, 2006). Cadmium was reported to affect different classes of adhesion molecules, i.e. ICAM-1, VCAM-1, PECAM-1 and VE-cadherins (Jiang *et al.*, 2002; Jeong *et al.*, 2004; Bertin & Averbeck, 2006; Prozialeck *et al.*, 2006; Seok *et al.*, 2006). Jiang *et al.* demonstrated that exposure of proximal tubule derived cell lines to 2 μM Cd for 4 hours resulted in a 2-fold induction in the expression of pro-inflammatory intercellular adhesion molecule-1 (ICAM-1) (Jiang *et al.*, 2002). Jeong *et al.* showed that cadmium stimulated the expression of ICAM-1 in cerebrovascular endothelial cells (Jeong *et al.*, 2004). In a study of Seok and coworkers, b.End.3 mouse brain endothelial cells were incubated with 2 μM $CdCl_2$ for 4 hours; cadmium exposure significantly increased the expression of ICAM-1 (Seok *et al.*, 2006).

Another adhesion molecule affected by cadmium is the vascular cell adhesion molecule-1 (VCAM-1) (Knoflach *et al.*, 2011). Knoflach *et al.* exposed ApoE-/- mice to 100 mg $CdCl_2$/L through drinking water for 12 weeks. VCAM-1 expression in the vessel wall was statistically higher in cadmium-fed mice than in controls (Knoflach *et al.*, 2011). Park and coworkers examined the effect of cadmium on the expression of VCAM-1 in b.End.3 mouse brain endothelial cells (Park *et al.*, 2009). The treatment with 3 and 10 μM Cd for 4 hours significantly increased VCAM-1 protein expression in a concentration-dependent manner (Park *et al.*, 2009).

Mousa administered a single injection of $CdCl_2$ (3 mg/kg b.w.) to rats and found that the expression of another adhesion molecule, platelet-endothelial adhesion molecule-1 (PECAM-1) in sinusoidal endothelial cells, decreased significantly 48 hours post-injection, which was followed by a significant increase 7 days post-injection (Mousa, 2004).

Cadherins are another cell adhesion molecules that might be affected by cadmium. This metal is able to disrupt cadherin-dependent cell-cell junctions (Prozialeck *et al.*, 2006). Human umbilical vein endothelial cells (HUVECs) were exposed for 15 hours to either 10 or 100 nM Cd; the localization of VE-cadherin was assessed (Prozialeck *et al.*, 2006). The results of the aforementioned study show that 10 nM Cd caused slight redistribution of VE-cadherin, while the cadmium concentration of 100 nM resulted in a significant reduction in the VE-cadherin at the cell-cell contacts, and the presence of gaps between cells (Prozialeck *et al.*, 2006).

CADMIUM AND iNOS

Inducible nitric oxide synthase (iNOS), a mediator of inflammation, is an inducible enzyme that causes the overproduction of nitric oxide during inflammation and tumor development (Lee & Lim, 2011). Lee and Lim used BNL CL.2 cells and treated them with $CdCl_2$ (10 μM) for 24 hours; the authors reported increased expression of iNOS after cadmium treatment as compared to control (Lee & Lim, 2011). Ramirez and Gimenez analyzed inflammatory mediators in resident peritoneal macrophages of mice chronically exposed to cadmium (15 ppm for 2 months) through drinking water. The authors found that iNOS synthesis was significantly induced in macrophages from cadmium treated mice (Ramirez & Gimenez, 2003). Moreover, the results of Alvarez and coworkers were in contrast to the aforementioned studies. The authors evaluated the effects of chronic exposure to cadmium (15 ppm for 3 months) on the expression of iNOS of rat prostate (Alvarez *et al.*, 2004). The results of that study showed no change in the expression of iNOS after the cadmium challenge (Alvarez *et al.*, 2004).

CADMIUM AND MMPs

Matrix metalloproteinases (MMPs) are metalloenzymes involved in many physiological and pathological processes (Kirschvink *et al.*, 2005; Lee & Lim, 2011; Yaghooti *et al.*, 2012). Gelatinases A (or MMP-2) and B (or MMP-9) were reported to play a predominant role in lung tissue remodeling and repair through degradation of extracellular matrix components, such as collagen and elastase (Kirschvink *et al.*, 2005). Proteolytic activity of MMPs was suggested to be related to pulmonary inflammation (Kirschvink *et al.*, 2005). Kirschvink *et al.* demonstrated in their study that cadmium nebulization ($CdCl_2$ 0.1%) in rats resulted in a significant increase in BALF MMP-9 and MMP-2 levels (Kirschvink *et al.*, 2005). Fievez *et al.* (2009) examined the effects of cadmium nebulization ($CdCl_2$ 0.1%) in rats on MMP-2-9/TIMP-1-2 imbalance. They found that cadmium induced a significant increase in BALF MMP-2, MMP-9 and TIMP-2 expression and/or activities, however, TIMP-1 was not detectable in any BALF samples (Fievez *et al.*, 2009). Kundu and coworkers exposed Swiss albino mice to sublethal dose of $CdCl_2$ (5 mg/kg b.w.) for different time periods (15, 30, 45 and 60 days) and analyzed the expression of MMP-2 and MMP-9 in lung cell extracts. The authors observed a significant expression of MMP-2, but not MMP-9 throughout the experimental period, suggesting that MMP-2 was one of the mediators of lung inflammation (Kundu *et al.*, 2009). Lee and Lim determined the expression of MMP-9 in $CdCl_2$-induced BNL CL.2 cells and found that MMP-9 activity was augmented after treatment with 10 μM $CdCl_2$ for 30 hours, compared to the control (Lee & Lim, 2011). In a recent study of Yaghooti *et al.*, the U-937 cell cultures were treated with different concentrations of cadmium (1, 10 and 50 μM $CdCl_2$) for 12 hours, and cellular secretions of MMP-9 and TIMP-1 were measured. The authors demonstrated that incubation of the U-937 cells with only highest applied cadmium concentration (50 μM) resulted in a significant increase in MMP-9 secretion. Cadmium at doses used in that study did not affect the TIMP-1 levels. Thus, cadmium appeared to disturb MMP-9/TIMP-1 balance in favor of proteolysis (Yaghooti *et al.*, 2012).

CADMIUM AND COX-2

Cyclooxygenase-2 (COX-2), prostaglandin 2 synthase, is an enzyme involved in the inflammatory process; it catalyzes the rate-limiting step in the formation of inflammatory prostaglandins from arachidonic acid (Shin *et al.*, 2003; Lee & Lim, 2011). COX-2 is undetected under physiological conditions (Miyahara *et al.*, 2004). A number of studies investigated the effect of cadmium on this enzyme expression at both mRNA and protein levels (Miyahara *et al.*, 2001; Choi *et al.*, 2002; Figueiredo-Pereira *et al.*, 2002; Ramirez & Gimenez, 2003; Shin *et al.*, 2003; Alvarez *et al.*, 2004; Rockwell *et al.*, 2004; Seok *et al.*, 2006; Kundu *et al.*, 2009; Lee & Lim, 2011).

In a study of Miyahara *et al.* the primary mouse osteoblastic cells were cultured with 1, 3 and 5 μM cadmium for 6 hours and COX-2 mRNA expression was markedly stimulated by cadmium at concentration of 1 μM and above (Miyahara *et al.*, 2001). Lee and Lim demonstrated that murine embryonic liver cells BNLCL.2 treated with 10 μM cadmium for 24 hours exhibited significantly higher expression of COX-2 as compared to control (Lee & Lim, 2011). Figueiredo-Pereira and coworkers treated mouse HT4 cells with a concentration of $CdSO_4$ of 1.5, 3, 15, 30 and 40 μM for 10, 16, 24, and 48 hours; the authors demonstrated time- and dose-dependent increase in COX-2 protein levels. Also $CdSO_4$ concentrations ranging between 3 and 30 μM caused significant induction of COX-2 mRNA (Figueiredo-Pereira *et al.*, 2002). Rockwell and coworkers also used mouse HT4 cells and treated them with 15 μM of cadmium for 24 hours; cadmium significantly increased COX-2 protein expression (Rockwell *et al.*, 2004). Another group of researchers showed that murine cerebrovascular endothelial cells bEnd.3 exposed to the concentrations of cadmium of 0.2, 2 and 20 μM exhibited significantly higher expression of COX-2 mRNA at 2 and 20 μM during 3 hours following the incubation (Seok *et al.*, 2006). Also the COX-2 protein expression was markedly increased in cells exposed to cadmium following 24-hour incubation (Seok *et al.*, 2006). Ramirez and Gimenez showed that mouse peritoneal macrophages from mice treated with 15 ppm Cd for 2 months through drinking water, exhibited markedly higher expression of COX-2 (Ramirez & Gimenez, 2003). Kundu and coworkers conducted a research, in which mice were given a sublethal dose of cadmium chloride (5 mg/ kg b.w.) once a week for different time periods (15, 30, 45 and 60 days). After that time the animals were sacrificed and their lungs were taken for analysis. The results of that study demonstrated

that cadmium caused the increased COX-2 expression throughout all the experimental periods (Kundu *et al.*, 2009). In a research of Choi *et al.* the Sprague-Dawley rats were administered 500 ppm cadmium through drinking water for 20 weeks. The COX activity level in platelets increased by 284 % in cadmium exposed group compared to controls (Choi *et al.*, 2002). Shin and coworkers showed that cadmium acetate in concentrations of 10, 50 or 100 μM caused the increase in the expression of COX-2 mRNA in human peripheral blood mononuclear cell (PBMC) cultures treated with cadmium during 4–24 hours (Shin *et al.*, 2003). However, one study demonstrated contradictory results as far as cadmium effect on COX-2 is concerned (Alvarez *et al.*, 2004). The Wistar rats were exposed to cadmium (15 ppm in drinking water) for 3 months. The expression of COX-2 in rat prostate of cadmium-treated rats did not differ statistically from that of controls (Alvarez *et al.*, 2004).

CADMIUM AND PGE_2

Prostaglandin E_2 (PGE_2), a product of COX-2 enzyme, is an inflammatory and immunomodulatory mediator in mammalian physiology (Ramirez & Gimenez, 2003). Several studies investigated cadmium effects on prostaglandin E_2 synthesis (Romare & Lundholm, 1999; Miyahara *et al.*, 2001; Figueiredo-Pereira *et al.*, 2002; Ramirez & Gimenez, 2003; Miyahara *et al.*, 2004; Seok *et al.*, 2006). All of these studies revealed the induction of PGE_2 synthesis due to cadmium exposure.

Romare and Lundholm demonstrated that basal PGE_2 production in untreated mouse calvaria cultures was very low (>20 pg/ml incubation medium). However, the presence of cadmium during incubation period caused an increased PGE_2 production (mean 132 pg/ml of incubation medium) (Romare & Lundholm, 1999). In a study of Miyahara *et al.* primary mouse osteoblastic cells were cultured with 1 or 3 μM Cd for 3, 6 and 9 hours. PGE_2 production was stimulated by cadmium in a dose- and time-dependent manner (Miyahara *et al.*, 2001). In another study by the same group of investigators, the dose-dependency of PGE_2 production was shown through a cadmium treatment of mouse osteoblastic cells (1, 2, 3, 4 and 5 μM) for 6 hours. Cadmium at 2 μM and above stimulated PGE_2 production (Miyahara *et al.*, 2004). Ramirez and Gimenez demonstrated that *in vivo* Cd exposure (15 ppm for 2 months) through drinking water caused higher PGE_2 synthesis in peritoneal macrophages as a consequence of increased COX-2 expression (Ramirez & Gimenez, 2003). Seok and coworkers showed time-dependency in PGE_2 production by murine brain endothelial cells bEnd.3 exposed to 2 μM $CdCl_2$ (Seok *et al.*, 2006). In another experiment, cadmium (0.2, 2 and 20 μM) was found to increase the release of PGE_2 significantly, 24 hours following the exposure and the maximal effect was observed at 2 μM of Cd (Seok *et al.*, 2006). Figueiredo-Pereira *et al.* showed in their study that mouse neuronal HT4 cells treated with increasing concentrations of cadmium for 24 hours exhibited a 360-fold increase in PGE_2 production as compared with a basal PGE_2 level in untreated cells (90 ng of PGE_2/mL of medium vs 0.25 ng of PGE_2/mL of medium). However, after a 48-hour cadmium incubation, the production of PGE_2 in cells exposed to 30 and 45 μM Cd was 3 times lower than in those exposed to 15 μM, probably due to poor cell survival caused by higher cadmium concentrations (Figueiredo-Pereira *et al.*, 2002).

CADMIUM AND CRP

CRP is a reliable marker of inflammation that raises several hundred fold in response to different inflammatory stimuli (Das, 2011). The high-sensitivity CRP (hs-CRP) assays detect concentrations accurately down to 0.3 mg/L and are especially useful in the assessment of risk of low-grade systemic inflammatory conditions (Das, 2011). Lin and coworkers conducted a cross-sectional study on the sample of 6497 US citizens aged 40-79 years, and found that higher urinary cadmium level was significantly associated with elevated blood CRP (≥2.2 mg/L) (Lin *et al.*, 2009). Hsu and colleagues examined in a cross-sectional study the relationship between blood Cd level and inflammation in 954 maintenance haemodialysis patients. The multivariate regression analysis showed that blood cadmium level was positively and significantly correlated with inflammatory risk (hs-CRP> 3 mg/L). The risk ratio of inflammation associated with a 10-fold increase in blood cadmium level was 1.388 (95%CI: 1.025–1.825, p=0.03) (Hsu *et al.*, 2009).

CADMIUM AS AN ANTI-INFLAMMATORY FACTOR

Although most of the reviewed literature demonstrated cadmium to be a pro-inflammatory factor, several studies suggest this metal to have non-inflammatory, or even anti-inflammatory properties (Bernhard *et al.*, 2006; Messner & Bernhard, 2010). Messner and Bernhard found no correlation between serum cadmium levels and CRP levels in humans, suggesting that increased serum Cd concentrations do not result in an increase in systemic inflammation markers (Messner & Bernhard, 2010). Bernhard *et al.* incubated primary human arterial endothelial cells with 1.5 μM cadmium for 6 and 24 hours. Using the microarray technology and real-time PCR, the authors demonstrated that a number of pro-inflammatory genes were down-regulated by cadmium, for example COX-2 and CXCL2 chemokine (Bernhard *et al.*, 2006). The results of Bernhard *et al.* suggest that cadmium suppresses inflammation and inhibits infiltration into the vessel wall (Bernhard *et al.*, 2006).

CONCLUSIONS

To sum up, most of the reviewed research findings suggest that cadmium in micromolar concentrations (especially in the range 1-10 μM) causes up-regulation of the mediators and markers of inflammation, such as NF-κB, AP-1, IL-6, TNF-α, IL-1β, IL-8, ICAM-1, VCAM-1, PECAM-1, MPO, iNOS, MMPs, COX-2, PGE_2, and CRP and seems to possess pro-inflammatory properties. However, it is worth mentioning that a contradictory or opposite hypothesis exists, which suggests cadmium to be an anti-inflammatory factor. Further research including detailed histological analyses should solve this discrepancy. Nevertheless, it appears that the main reason for these contradictory findings is the experimental setup: different biological systems analyzed and different doses of cadmium applied.

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