Environmental Pollution 235 (2018) 429–434

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Gut as a target for cadmium toxicity☆

Alexey A. Tinkov [a, b, c, *], Viktor A. Gritsenko [c], Margarita G. Skalnaya [b], Sergey V. Cherkasov [c], Jan Aaseth [d, e], Anatoly V. Skalny [a, b, f]

[a] Yaroslavl State University, Sovetskaya St., 14, Yaroslavl 150000, Russia
[b] Peoples' Friendship University of Russia (RUDN University), Miklukho-Maklay St., 10/2, Moscow 117198, Russia
[c] Institute of Cellular and Intracellular Symbiosis, Russian Academy of Sciences, Orenburg, 460008, Russia
[d] Innlandet Hospital Trust, 2226 Kongsvinger, Norway
[e] Inland Norway University of Applied Sciences, Terningen Arena, 2411 Elverum, Norway
[f] Orenburg State University, Pobedy Ave., 13, Orenburg 460018, Russia

ARTICLE INFO

Article history:
Received 12 November 2017
Received in revised form
26 December 2017
Accepted 28 December 2017

Keywords:
Cadmium
Gut microbiota
Lipopolysaccharide
Bacteroides
Firmicutes

ABSTRACT

The primary objective of the present study was to review the impact of Cd exposure on gut microbiota and intestinal physiology, as well as to estimate whether gut may be considered as the target for Cd toxicity. The review is based on literature search in available databases. The existing data demonstrate that the impact of Cd on gut physiology is two-sided. First, Cd exposure induces a significant alteration of bacterial populations and their relative abundance in gut (increased *Bacteroidetes*-to-*Firmicutes* ratio), accompanied by increased lipopolysaccharide (LPS) production, reflecting changed metabolic activity of the intestinal microbiome. Second, in intestinal wall Cd exposure induces inflammatory response and cell damage including disruption of tight junctions, ultimately leading to increased gut permeability. Together with increased LPS production, impaired barrier function causes endotoxinemia and systemic inflammation. Hypothetically, Cd-induced increase gut permeability may also result in increased bacterial translocation. On the one hand, bacteriolysis may be associated with aggravation of endotoxemia. At the same time, together with Cd-induced impairment of macrophage inflammatory response, increased bacterial translocation may result in increased susceptibility to infections. Such a supposition is generally in agreement with the finding of higher susceptibility of Cd-exposed mice to infections. The changed microbiome metabolic activity and LPS-induced systemic inflammation may have a significant impact on target organs. The efficiency of probiotics in at least partial prevention of the local (intestinal) and systemic toxic effects of cadmium confirms the role of altered gut physiology in Cd toxicity. Therefore, probiotic treatment may be considered as the one of the strategies for prevention of Cd toxicity in parallel with chelation, antioxidant, and anti-inflammatory therapy.

1. Introduction

Cadmium is an environmental pollutant possessing serious health hazards (Satarug et al., 2011). In particular, Cd pollution is widespread through Europe with the highest levels in sediments and stream water being observed in Germany and Slovakia, whereas topsoil Cd levels were maximal in Greece, Italy, France, Austria, Ireland (Pan et al., 2010). The mean weekly intake of Cd in European adults accounts for 2.5 μg/kg (Nawrot et al., 2010). Cd exposure is also found to be high in China (Zhang et al., 2016). At the same time, the highest Cd content in rice was detected in Bangladesh and Sri-Lanka (Meharg et al., 2013). Although some studies demonstrate a significant reduction in Cd exposure (USA), further reduction is required (Tellez-Plaza et al., 2012a,b).

High social costs of Cd exposure are related to its role in various diseases. In particular, it has been demonstrated that Cd is associated with cancer (Adams et al., 2011; Hartwig, 2013), diabetes mellitus (Tinkov et al., 2017), cardiovascular diseases (Tellez-Plaza et al., 2012a,b), chronic kidney disease (Ferraro et al., 2010), osteoporosis (Kazantzis, 2004), liver disease (Hyder et al., 2013), neurodegeneration (Min and Min, 2016), adverse neurodevelopmental outcome (Wang et al., 2016), and other diseases (Satarug et al., 2011). It has been estimated that high Cd exposure significantly

☆ This paper has been recommended for acceptance by David Carpenter.

* Corresponding author. Yaroslavl State University, Sovetskaya St., 14, Yaroslavl 150000, Russia.
E-mail address: tinkov.a.a@gmail.com (A.A. Tinkov).

https://doi.org/10.1016/j.envpol.2017.12.114
0269-7491/

increases mortality by 17% (Nawrot et al., 2010).

Traditionally, the variety of adverse health effects attributed to Cd exposure has been explained by the general mechanisms of metal toxicity. In particular, it has been reported that Cd is capable of induction of oxidative stress (Liu et al., 2009), inflammation (Olszowski et al., 2012), endoplasmic reticulum stress (Biagioli et al., 2008), genomic instability (Rani et al., 2014), and essential metal dyshomeostasis (Moulis, 2010). Certain effects of the metal are associated with its effect as an endocrine disruptor (Takiguchi and Yoshihara, 2006). However, further investigations of mechanisms of Cd toxicity is highly required for assessment and prevention of its harmful effects.

Gut microbiota is known to play a significant role in a number of physiological functions (Tremaroli and Bäckhed, 2012), including regulating immunity (Round and Mazmanian, 2009) and mineral metabolism (Skrypnik and Suliburska, 2017). Qualitative, quantitative, or functional (metabolic) disturbances of the gut microbiota may mediate the development numerous diseases (Marchesi et al., 2015; Scott et al., 2015). Microbiota has been considered as a target for environmental pollutants including persistent organic pollutants, antibiotics, pesticides, as well as heavy metals (Jin et al., 2017). However, existing data and reviews on the possible role of gut dysbiosis in mediating Cd toxicity are insufficient.

Therefore, the primary objective of the present study was to review the impact of Cd exposure on gut microbiota and intestinal physiology as well as estimate whether gut may be considered as the target for Cd toxicity.

1.1. Cd and gut microbiota

Gut microbiota is considered to be an important target mediating toxic effects of heavy metals including cadmium (Jin et al., 2017). The role of gut microbiota as a protective factor of Cd toxicity was indicated by Breton et al. (2013), who observed a significant increase in blood, liver, kidney, and spleen Cd content, as well as MT1 and MT2 expression in duodenum and colon in germ-free mice treated with Cd (Breton et al., 2013a). Certain studies have demonstrated the impact of chronic (and subchronic) and short-term Cd exposure on gut microbiome physiology in laboratory animals of different age.

Cd exposed (42 days) adult rats were characterized by a significant reduction in anaerobic, and also aerobic, and lactic bacteria in the gut (Jafarpour et al., 2015). Moreover, Cd induced specific changes in gut microbiota on family and genus levels. An earlier study demonstrated a significant dose-dependent reduction in *B. cereus*, *Lactobacillus spp*, *Clostridium spp*, *E. coli* intestinal populations in mice exposed to Cd in drinking water for 45 days (Fazeli et al., 2011). It has been also shown that Cd exposure for 8 weeks resulted in a significant dose-dependent increase in the relative abundance of Actinobacteria in caecum of mice, whereas the changes in *Bacteroidetes* and *Firmicutes* were not significant. At the family level, caecal flora was characterized by a dose-dependent increase in the relative number of Coriobacteriaceae, Lactobacillaceae, whereas the percent of Lachnospiraceae decreased. The changes in fecal bacteria in Cd-exposed mice were less pronounced (Breton et al., 2013). Zhai et al. (2017) have also demonstrated a significant increase in relative abundance of *Alistipes* and *Odoribacter* genera, whereas *Mollicutes* and unclassified *Ruminococcaceae* were characterized by a significant Cd-induced reduction in adult male C57black/6 mice after the same period of metal exposure (Zhai et al., 2017). It is notable that Cd-induced alterations in microbiota are more pronounced in the first 4 weeks of exposure as compared to the latter 4 weeks. Kim et al. (2015) also demonstrated that oral Cd treatment reduces bacterial diversity of the gut as well as alters *Firmicutes* to *Bacteroidetes* ratio. It is also notable that the observed NF-kB activation and proinflammatory cytokine secretion was at least partially dependent on Cd-induced alteration of gut microbiome, as germ-free mice were less prone to proinflammatory response to Cd exposure (Kim et al., 2015). The observed changes in the gut persisted for a long time after elimination of the agent. It is also notable, that transfer of gut microbiome to Cd-unexposed mice resulted in similar inflammatory and allergic responses, whereas no changes were detected in germ-free mice (Kim et al., 2017). These findings are generally in agreement with the earlier observation of increased intestinal permeability to macromolecules in Cd-exposed mice (28 days) (Kim et al., 2014). Liu et al. (2014) demonstrated that administration of the increasing doses of Cd significantly reduced intestinal bacterial populations as well as decreased the Firmicutes to Bacteroidetes ratio starting from 3 week of exposure. The number of *Bifidobacteria* also decreased starting from the 1 week of Cd exposure, whereas the significant dose-dependent reduction of lactobacilli population was detected only after 3 weeks of exposure. These changes were also accompanied by increased production of TNFα and alteration of genes involved in the bacterial metabolism of short-chain fatty acids (SCFAs). Correspondingly, incubation of the cultured fecal microbiota with Cd in vitro resulted in a significant decrease in cell viability (Liu et al., 2014). Oppositely, another study demonstrated a significant decrease in *Bacteroides* abundance in response to Cd treatment for 8 weeks. At the same time, Cd exposure was shown to reduce SCFAs concentration in the fecal pellet (Li et al., 2016).

In parallel with altered intestinal biodiversity under chronic Cd exposure, short term Cd treatment also affects gut microbiome physiology. In particular, it has been demonstrated that Cd exposure induces a significant shift in bacterial proteome starting from 15 min of exposure. Based on these findings the authors have proposed the characteristic changes of protein expression in gut microbiota may be related to three temporal response patterns to Cd exposure: resistance, adaptation, sustained tolerance (Lacerda et al., 2007). In an earlier in vitro study Wang and Crowly also demonstrated Cd-induced alteration of global gene expression. Of note, in line with the impact on energy metabolism, cell cycle, transport and binding protein genes, Cd exposure for 0, 5, 15, and 25 min resulted in up-regulation of genes that may be related to biosynthesis/transport of lipopolysaccharides (Wang and Crowley, 2005). These data are of great importance, being indicative of the nearly immediate effects of Cd on gut microbiota.

Early life low-dose Cd exposure also significantly affected the quantity and biodiversity of the gut microbiome. In particular, at 8-week age Cd-exposed male (but not female) mice were characterized by a significant increase in Bacteroides and a concomitant decrease in Firmicutes populations. At the genus levels, the most significant decrease was detected in *Bifidobacterium* and *Prevotella* populations. It is also notable that the population of Cd-accumulating *Sphingomonas* was significantly higher in Cd-exposed animals. Interestingly, the observed changes in gut microbiome were associated with increased adiposity in Cd-treated mice. This consequence of Cd-induced alteration of the microbiome was confirmed by the observed increase in adipose tissue mass accumulation after transfer of fecal flora from Cd-exposed to Cd-unexposed mice. Moreover, pretreatment of mice with Gram-negative targeting antibiotics prevented Cd-induced increase in adiposity (Ba et al., 2017). Another study demonstrated a significant decrease in caecal *Firmicutes* in response to Cd exposure in 5-week-old C57BL/6 male mice, whereas *Bacteroidetes* and γ-proteobacteria were unaffected. These changes were associated with alteration of energy homeostasis genes (fatty acids synthesis and transport, triglyceride synthesis) in liver that may be related to LPS-induced up-regulation of proinflammatory gene expression (Zhang et al., 2015).