Biometals
DOI 10.1007/s10534-015-9823-2

Mercury and metabolic syndrome: a review of experimental and clinical observations

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Received: 17 November 2014 / Accepted: 15 January 2015
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Abstract A significant interrelation between heavy metal exposure and metabolic syndrome (MetS) development has been demonstrated earlier. Despite the presence of a number of works aimed at the investigation of the role of Hg in MetS development, the existing data remain contradictory. Therefore, the primary objective of the current work is to review the existing data regarding the influence of mercury on universal mechanisms involved in the pathogenesis of the development of MetS and its components. The brief chemical characterization of mercury is provided. The role of mercury in induction of oxidative stress has been discussed. In particular, Hg-induced oxidative stress may occur due to both prooxidant action of the metal and decrease in antioxidant enzymes. Despite the absence of direct indications, it can be proposed that mercury may induce endoplasmic reticulum stress. As it is seen from both in vivo and in vitro studies, mercury is capable of inducing inflammation. The reviewed data demonstrate that mercury affects universal pathogenetic mechanisms of MetS development. Moreover, multiple investigations have indicated the role of mercury in pathogenesis of MetS components: dyslipidemia, hypertension, insulin resistance, and obesity to a lesser extent. The present state of data regarding the interrelation

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Published online: 30 January 2015

between mercury and MetS denotes the following perspectives: (1) Further clinic-epidemiologic and experimental studies are required to estimate the association between mercury exposure and the development of MetS components, especially obesity; (2) Additional investigations of the possible effect of organism's mercury content modulation on MetS pathogenesis should be undertaken.

Keywords Mercury · Toxicity · Obesity · Insulin resistance · Hypertension · Dyslipidemia · Atherosclerosis

Introduction

Metabolic syndrome (MetS) is a complex metabolic disturbance associated with obesity (Eckel et al. 2005). Final understanding of MetS was formed by Reaven in 1988 (Reaven 1988; 1993), while the conception of MetS existed for more than 80 years due to multiple observations (Cameron et al. 2004). Despite the presence of a great number of MetS definitions (Oda 2012), general criteria for this state are dyslipidemia, arterial hypertension, glucose dyshomeostasis and insulin resistance, and obesity (Kassi et al. 2011). Some classifications propose a number of other additive criteria like impaired uric acid metabolism, prothrombotic factors, inflammatory and endothelial dysfunction markers, and microalbuminuria (Parikh and Mohan 2012).

MetS has a significant socio-economic impact due to its strong relation to mortality. Particularly, a significant association between the presence of MetS and cardio-vascular mortality has been indicated in Russia (Sidorenkov et al. 2010), Finland (Lakka et al. 2002), Japan (Kondo et al. 2011), and USA (Malik et al. 2004). At the same time, the incidence of MetS has been increased rapidly from 1999 to 2006 (Mozumdar and Liguori 2011). Despite a certain decrease (from 25.5 to 22.9 %) in 2010 (Beltrán-Sánchez et al. 2013), the incidence of MetS in adults remains high. It is also important to note the prevalence of MetS in children and adolescents also is increasing to high levels (Friend et al. 2013).

Due to a presence of multiple components of the MetS, its pathogenesis involves a wide number of mechanisms. However, current data allow to mark out universal mechanisms taking part both in development of MetS itself and its components. Particularly, a tight relationship between MetS and oxidative stress has been demonstrated (Furukawa et al. 2004; Roberts and Sindhu 2009; Youn et al. 2014). This process also plays a significant role in pathogenesis of obesity (Matsuzawa-Nagata et al. 2008; Fernández-Sánchez et al. 2011), insulin resistance (Matsuzawa-Nagata et al. 2008; Ceriello and Motz 2004), hypertension (Zalba et al. 2001; Vaziri and Rodríguez-Iturbe 2006) and dyslipidemia (Rizzo et al. 2009; Matsuda and Shimomura 2013). Endoplasmic reticulum stress (ERS) is also postulated to be a universal mechanism playing a significant role in the development of a number of MetS-related pathologies (Bánhegyi et al. 2007). Despite limited data indicating its role in MetS (Sage et al. 2012; Xia et al. 2012), a wide number of works have demonstrated the importance of ERS in pathogenesis of individual components of MetS (Ozcan et al. 2004; Young et al. 2012; Cnop et al. 2012; Basseri and Austin 2012; Santos et al. 2014). At the same time, inflammatory reaction is considered to be one of the key mechanisms of MetS development (Romeo et al. 2012). It is also important to note that inflammation is interrelated both with oxidative (Pillarisetti and Saxena 2004) and ERS (Zhang and Kaufman 2008).

During a long period of time genetic predisposition, excessive caloric consumption and sedentary lifestyle were considered to be the main risk factors of MetS development (Zhang et al. 2009). However, recent research indicated a substantial role of environmental factors in the development of this syndrome (Lind et al. 2013). Particularly, a significant interrelation between heavy metal exposure and MetS development has been demonstrated (Moon 2014).

In particular, a wide investigation of 2,114 adults occupationally not exposed to Hg compounds demonstrated a significant relationship between blood mercury levels and body mass index (BMI), waist circumference, systolic and diastolic arterial pressure, fasting blood glucose and triglycerides (TG) (Eom et al. 2014). Investigation of hair metal content in 343 people also indicated that persons suffering from MetS are characterized by a significant 70 % increase in hair mercury in comparison to healthy subjects. Moreover, statistical analysis revealed a close relationship between hair mercury levels and the risk of MetS development (Park et al. 2009). Within the National Health and Nutrition Examination Survey (NHANES)

2003–2004 analysis a substantial interrelationship between the increasing mercury levels and alanine aminotransferase (ALT) has been shown, that can be indicative of non-alcoholic fatty liver disease (NAFLD) (Cave et al. 2010). A close pathogenetic interplay between NAFLD and MetS (Vanni et al. 2010) may also be indicative of the role of mercury in MetS development. At the same time, the Korea National Health and Nutrition Examination Survey (KNHANES) 2005–2010 data have demonstrated the lack of significant relationship between blood mercury levels and both MetS and its individual components (Lee and Kim 2013). Therefore, despite the presence of a number of works aimed at the investigation of the role of Hg in MetS development, the existing data remain contradictory.

Moreover, investigation of various aspects of mercury toxicology is particularly important due to a wide distribution of mercury compounds in the environment (Bender et al. 2013). In particular, recent data have demonstrated a 3-fold increase in mercury level in the global ocean in comparison to pre-anthropogenic conditions (Lamborg et al. 2014).

Therefore, the primary objective of the current work is to review the existing data regarding the influence of mercury on universal mechanisms involved in the pathogenesis of the development of MetS and its components.

Brief chemical characterization of mercury

In view of the purpose of the review, we shall discuss only the basic physio-chemical characteristics of mercury that are directly related to its biological action (discussed further below).

Mercury $_{80}$Hg (atomic mass 200.59) along with Zinc ($_{30}$Zn) and Cadmium ($_{48}$Cd) is an element of the 12th group of the periodic system. Several mercury isotopes, including the most stabile Hg^{196}, Hg^{198}, Hg^{199}, Hg^{200}, Hg^{201}, Hg^{202} have been reported (Cotton et al. 1999). In the ground state, the mercury atom has an electronic configuration of $[Xe]4f^{14}5d^{10}6s^2$. The presence of "inert" $6s^2$ electronic pair determines the relatively low chemical reactivity of mercury (Greenwood and Earnshaw 1997).

As the 5d-sublevel of mercury is occupied, the ascription of mercury to d-elements is generally formal. In fact, Hg is already not a transition metal. High stability of d^{10} electron shell determines the difficulty of the third electron detachment (Eliav et al. 1995). A high value of the third ionization potential is indicative of this property (3,300 kJ/mol). Mercury virtually does not form compounds with the unoccupied d-sublevel. Consequently, the oxidation rate of +2 is the most stable for mercury atom. At the same time, in contrast to zinc and cadmium, for which +2 oxidation rate is more characteristic, in a number of compounds mercury may have the oxidation number of +1 (Kunkely and Vogler 1989). The presence of occupied d-sublevel increases the covalent character of mercury compounds, particularly halides. The formation of di-, tri- and tetranuclear clusters (Hg_2^{2+}, Hg_3^{2+}, Hg_4^{2+}) (Gillespie et al. 1984) is characteristic for mercury due to the presence of covalent Hg–Hg bonds. In accordance with the expressed ability to form covalent bonds, mercury forms a wide spectrum of metalloorganic compounds (Cotton et al. 1999; Greenwood and Earnshaw 1997). A wide number of organic and inorganic mercury compounds, being formed in accordance with the above mentioned principles, are present in the environment and possess toxic properties. However, the detailed description of these compounds is provided in a number of excellent reviews (Risher et al. 2002; Syversen and Kaur 2012) and is not a primary objective of the current review.

At the opposite side, due to the ability to complexation, mercury bears similarity to transition metals. The most common coordination numbers for linear and tetrahedral complexes are 2 and 4, respectively, with the latter being more preferable (Gillespie 1972). Other coordination numbers (5, 8) are also possible, however, they occur rarely (Cotton et al. 1999). The strongest complexes are formed with ligands containing nitrogen, phosphorus, sulfur, and halogens (Cotton et al. 1999; Greenwood and Earnshaw 1997). The ability of mercury to form strong bonds with thiol groups and sulfur-containing ligands has been shown. Mercuric ion (Hg^{2+}) easily forms complexes like $[HgR_2S]^+$ with dialkylsulfides R_2S (Ravichandran 2004), whereas $[HgHal_n]^{n-2}$ complexes are formed during the interaction with easily formed complexes with soft ligands like ammonia, amines, cyanide and halogen ions (Grdenic 1965).

According to Pearson's conception, mercury cations, Hg^{2+} and Hg_2^{2+} are related to the group of soft acids. These are the electron acceptors with high

polarizability, low electronegativity and large ionic radius (0.116 nm for Hg^{2+} and 0.111 nm for Hg^{+}), that is very characteristic for ions with d^{10} electronic configuration (Pearson 1963, 1968). Acid–base interaction according to the principle of hard and soft acids and bases occurs in such a way when soft acids react predominantly with soft bases. Reaction between Hg(II) and thiocyanate ions may serve as the most typical example of such interaction. In particular, in the complex $[Hg(SCN)_4]^{2-}$ the central atom is coordinated with the ligands through more "soft" sulfur atom, but not through more "hard" nitrogen atom (Ghosh et al. 2007).

Due to the above mentioned properties mercury interacts with –SH groups of biologically active compounds in vivo. Particularly, the ability of mercury to react with amino acids (Van der Linden and Beers 1974), glutathione (Oram et al. 1996; Mah and Jalilehvand 2010), reduced coenzyme A, acyl coenzyme A (Gradinaru et al. 2011), and a number of proteins (Keizo and Yasuo 1979; Bagger et al. 1991; Bramanti et al. 1999) has been demonstrated earlier. Such behavior of mercury and its compounds predetermines its biological action, with one of the aspects being discussed later.

Influence of mercury on universal pathogenetic mechanisms

Mercury and oxidative stress

Due to its physic-chemical properties, mercury is an inducer of oxidative stress in biological systems. Particularly, it has been demonstrated that persons being occupationally exposed to mercury (a 40-fold elevation in mercury exposure in relation to the controls) are prone to oxidative stress development. The latter may be identified by an increase in 8-hydroxy-2′-deoxyguanosine (a marker of oxidative DNA damage) (8-OH-dG) and a decrease in antioxidant levels in serum (Chen et al. 2005). Similar data were obtained during the investigation of mercury-exposed workers of chloroalkali factory (Al-azzawie et al. 2013). At the same time, a tight interrelation between mercury exposure and oxidative stress development in fish-eating communities of the Brazilian Amazon has been shown (Grotto et al. 2010). Interesting results have been demonstrated after the investigation of mercury miners and non-exposed workers. In particular, blood mercury levels in miners with large post-exposure period did not differ significantly from those observed in the control group. However, the miners were characterized by higher urine thiobarbituric acid reactive substances (TBARS) concentration when compared to the unexposed controls. These observations allowed the authors to propose that prolonged mercury exposure may increase free-radical oxidation processes even after the elimination of the agent (Kobal et al. 2004). A dose-dependence between breast milk and infant urine mercury levels and urinary TBARS and 8-OH-dG concentrations indicate a significant impact of breast milk mercury on oxidative stress development in infants (Al-Saleh et al. 2013). Oppositely, no significant association between blood mercury levels and oxidative stress biomarkers has been revealed in a cohort of premenopausal women with low exposure levels (Pollack et al. 2012).

Experimental studies confirm the clinic-epidemiological data. It has been shown that intraperitoneal injection of 1 mg/kg methylmercury resulted in intensified lipid peroxidation (LPO) in various brain regions (Zahir et al. 2006). Similar data indicating the induction of renal phospholipid peroxidation were obtained after subcutaneous injection of methylmercury and mercuric chloride in rats (Shinada et al. 1990). Subcutaneous injection of mercury also resulted in a dose-dependent intensification of LPO in other rat organs and tissues (Yonaha et al. 1983; Lin et al. 1996; Huang et al. 1996). The results of the studies involving intragastric administration of mercury compounds were in agreement with the above mentioned studies (Mahboob et al. 2001). Subcutaneous injection of 2 mg/kg methylmercury in suckling rat pups induced the development of oxidative stress, as estimated by increased hepatic TBARS levels, decreased total thiol content and antioxidant system depression. Peroral administration of mercuric chloride also led to an increase in blood plasma TBARS content in Wistar rats (Hijova et al. 2005). Analysis of various porcine organs from Hg-contaminated area revealed the state of oxidative stress in comparison to the samples from non-Hg-contaminated area (Chen et al. 2006a, b, c, d). At the same time it is notable that perinatal treatment with 3 mg/kg methylmercury did not result in significant increase in rat offspring brain TBARS levels (Watanabe et al. 1999).

Investigations using different cell cultures also indicated the development of mercury-induced oxidative stress. Particularly, treatment with 5 and 10 μM methylmercury during 1–6 h resulted in a significant F2-isoprostanes' concentration increase in astrocytes culture (Yin et al. 2007).

Mechanisms of mercury-induced oxidative stress

According to the classic definition by Helmut Sies, oxidative stress is represented by an activation of free radical oxidation processes on a background of depressed antioxidant system (Sies 1997). Being a potent promotor of oxidative stress, mercury affects both components (Valko et al. 2005) (Fig. 1).

Prooxidant action of mercury

The influence of different mercury compounds on reactive oxygen species' (ROS) production has been demonstrated in multiple ex vivo studies. Particularly, it has been shown that incubation of hypothalamic neural cell line GT1-7 with 10 mM methyl mercury for 3 h was accompanied by a significant intensification of ROS generation, as assessed by increased 2,7-dichlorofluorescin diacetate fluorescence (Sarafian et al. 1994). Later it has been noted that this effect is dose-dependent in the concentration range of 1–5 μM (Ni et al. 2010). Along with total intensification of ROS production, Shanker et al. have demonstrated the impact of individual free radical species in this process. Particularly, it has been shown that, incubation of astrocytes in the presence of methylmercury resulted in hydrogen peroxide, superoxide anion, and peroxynitrite hyperproduction (Shanker et al. 2004). Moreover, indications of mercury-induced activation of xanthine oxidase have been obtained using AS52 cells (Ariza et al. 1998). It is notable that xanthine oxidase is the source of hydrogen peroxide and superoxide anion radical production (Porras et al. 1981). Along with increased xanthine oxidase activity, a number of researchers have demonstrated mercury-mediated activation of NADPH-oxidase (Aguado et al. 2013; Rizzetti et al. 2013), also being the superoxide producer (Hoffman and Autor 1980). The influence of mercury on mitochondrial generation of ROS has also been investigated. Particularly, a 4 and 2-fold mercury-induced increase in hydrogen peroxide generation by ubiquinol-cytochrome c reductase and NADH-dehydrogenase of the respiratory chain has been demonstrated respectively (Lund et al. 1991). At the same time, some observations indicated a suppressive impact of mercury treatment on superoxide production in activated murine peritoneal macrophages (Lison et al. 1988).

It is notable that prooxidant properties of mercury may be manifested during its interaction with biopolymers. Particularly, complexes of mercury with various thiols and glutathione have been shown to possess redox activity (Miller and Woods 1993). This observation has been confirmed by the indications of the ability of Hg(II)-$[GSH]_2$ complex to superoxide anion production (Aliaga et al. 2010). Similar data have been received during the investigation of mercury's influence on hemoglobin-catalyzed LPO (Ribarov et al. 1983). More details on prooxidative action of mercury and its organic compounds are described in an excellent review by Milaeva et al. (2004).

Influence of mercury on antioxidant system components

Glutathione system

Taking into account a high affinity of mercury to thiol groups, glutathione is one of the main antioxidants being impaired by mercury exposure.

Multiple investigations using cell cultures have indicated that mercury treatment results in a significant decrease in reduced glutathione (GSH) levels (Lee et al. 2001; James et al. 2005; Chang and Tsai 2008). Moreover, in an in vivo experiment it has been shown that prenatal mercury exposure leads to altered glutathione system ontogenesis and delayed age-related increase in brain GSH levels (Stringari et al. 2008). However, contradictory data have been obtained after mercuric chloride injection through the hepatic portal vein. Particularly, this manipulation was followed by a significant increase in hepatic and renal glutathione levels (Sin et al. 1989). At the same time, prolonged peroral administration of methylmercury in rats resulted in elevated glutathione level in kidney cortex and increased activity of γ-glutamylcysteine synthetase, the rate-limiting enzyme in glutathione synthesis (Woods and Ellis 1995). The respective effects were observed in human subjects. In particular, long-term occupational exposure to mercury in miners was followed by a significant

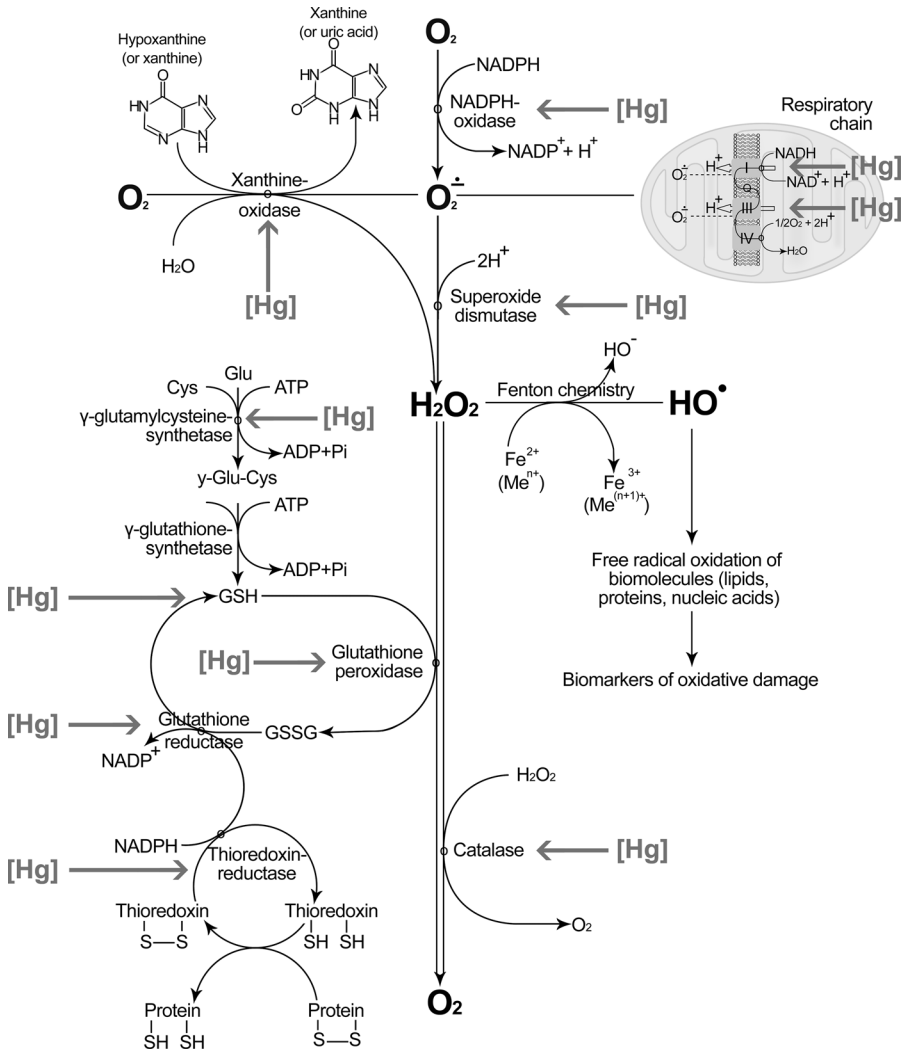

Fig. 1 A hypothetical scheme of mercury's influence on oxidative stress development by modulation of prooxidant and antioxidant enzyme activities. *Arrows* indicate the estimated fact of mercury's influence on a specific enzyme or compound. It is proposed that mercury increases NADPH-oxidase and xanthine oxidase activity leading to excessive production of superoxide anion radical. Possible positive influence of mercury on mitochondrial (I and III respiratory chain components) generation of superoxide should also be kept in mind. Intensity of the generated superoxide dismutation may be decreased due to Hg-induced SOD inhibition. Possible inhibition of catalase activity may lead to impaired hydrogen peroxide detoxification. The latter may take part in Fenton-like reactions being a precursor of much more reactive hydroxyl radical. Despite the possibility of mercury-induced increase in γ-glutamylcysteine synthetase and activation of glutathione synthesis, Hg-treatment presumably decreases GPx and GR activity. The latter also may result in decreased hydrogen peroxide decomposition. Thioredoxin reductase is also supposed to be one of the targets of mercury toxic action

increase in glutathione levels in haemolysed erythrocytes (Kobal et al. 2008).

In spite of affection glutathione levels, mercury is a potent modulator of glutathione-dependent enzymes like glutathione peroxidase (GPx) and glutathione reductase (GR). Specifically, it has been demonstrated that methylmercury decreases GPx activity in rodent liver (Hirota et al. 1980; Farina et al. 2004) and brain (Franco et al. 2009), as well as in cell cultures (Franco et al. 2009; Farina et al. 2009). The results by Usuki et al. have indicated that methylmercury exposure leads to degradation of GPx1 mRNA both in animal tissues and cell cultures (Usuki et al. 2011). Mercuric chloride also reduced GPx activity in different organs of laboratory

rodents (Black et al. 1979; Wada et al. 1976). Oppositely, data indicating an increase in GPx activity in mercury-exposed miners are present (Chen et al. 2006a, b, c, d).

GR activity also has been shown to be decreased following a 16–24 h methylmercury treatment in cell culture (Cuello et al. 2010). However, the results of in vivo study failed to reveal a significant mercury-induced decrease in GR activity in rat erythrocyte hemolysates, whereas micromolar concentrations of mercuric nitrate added to hemolysates in vitro resulted in a clear inhibition of the enzyme (Mykkanen and Ganther 1974). As in the case of glutathione, prenatal mercury treatment resulted in delayed increase in murine brain GPx and GR activity (Stringari et al. 2008). Occupational exposure to mercury vapors also resulted in a significant GR activity decrease in comparison to the control unexposed group (Zabiński et al. 2000).

Superoxide dismutase (SOD)

SOD catalyzes the dismutation of superoxide leading to generation of hydrogen peroxide being less reactive (McCord and Fridovich 1969). As many other proteins, this enzyme is susceptible to mercury influence. The investigation by Benov et al. has demonstrated that mercury intoxication is accompanied by SOD inactivation (Benov et al. 1990). Moreover, a decrease in mitochondrial and cytosolic Cu, Zn-SOD levels has been detected in mercury-treated mice (García-Sevillano et al. 2014). It is also estimated that different mercury compounds are inactivators of both Cu, Zn-SOD and Mn-SOD in vitro, whereas Mn-SOD is more susceptible to inhibitory action of methylmercury in vivo. The obtained data indicate that this inhibition was not associated with decreased protein mRNA expression (Kumagai et al. 1997a, b).

In contrast, data indicating an increase in renal Mn-SOD content following mercury-exposure has been provided. However, this qualitative elevation was accompanied by a decreased enzyme activity (Kumagai et al. 1997a, b). A study using AS52 cells has also demonstrated a significant 2-fold increase in Cu, Zn-SOD activity following 1 μM mercury treatment (Ariza et al. 1998). It has been shown later that mercury positively regulates both Cu, Zn-SOD and Mn-SOD mRNA levels in C2C12-DMPK160 cells (Usuki et al. 2011). Mercury vapor exposure also resulted in Cu, Zn-SOD activation in murine lungs, whereas Mn-SOD activity decreased (Shimojo et al. 1996). Interesting data regarding the influence of peroral administration of mercuric chloride on SOD activity have been obtained by Bando et al. (2005). Particularly, the first day of mercury exposure resulted in an increase both in Cu, Zn-SOD and Mn-SOD activity in liver homogenates. Further treatment with mercury led to a significant decrease in SOD activity in comparison to the control values (Bando et al. 2005).

Investigation of human subjects confirmed the influence of mercury on SOD activity. In particular, persons being exposed to mercury for a long period of time (7–32 months) were characterized by a significant decrease in erythrocyte SOD activity in relation to the control subjects (Zabiński et al. 2000). This observation has been confirmed by later studies (Abdel-Hamid et al. 2001). In contrast, the investigation of female workers exposed to mercury vapors have detected a slight increase in erythrocyte SOD activity along with the creatinine-corrected concentration of Hg in urine (Perrin-Nadif et al. 1996).

Catalase

In investigations using cultivated brain cells have indicated that treatment with 100 nM methylmercury results in decreased catalase activity (Sorg et al. 1998). These data correspond to earlier observations of inhibitory action of mercury in relation to erythrocyte catalase ex vivo (Ribarov et al. 1982). Peroral administration of methylmercury also resulted in hepatic and especially renal catalase inhibition in laboratory rats (Yasutake et al. 1997; de Freitas et al. 2009). Moreover, a tendency to a decrease in erythrocyte catalase has been observed in mercury-treated animals (Barcelos et al. 2011).

Investigations of various groups of human subjects have provided contradictory data regarding the interaction "mercury-catalase". Particularly, a decreased catalase activity has been revealed in mercury-exposed women living in contaminated Amazon areas in comparison to the respective control group (Pinheiro et al. 2008). However, a number of studies have indicated a positive relationship between an organism's mercury levels and catalase activity (Queiroz et al. 1998; Perrin-Nadif et al. 1996).

Thioredoxin system

Thioredoxins are small proteins containing free sulfhydryl groups and, consequently, being a target for mercury ions (Holmgren and Lu 2010). It has been shown that mercury more intensively oxidizes thioredoxins 1 and 2 than copper, iron, nickel and zinc (Hansen et al. 2006). Apart from Hg-mediated oxidation of trioredoxin sulfhydryl groups different concentrations of mercuric chloride decrease thioredoxin 1 content in human monocytes (Wataha et al. 2008).

Along with direct action on thioredoxins, mercury significantly influences thioredoxin reductase (TRXR) activity. Particularly, an inhibitory action of different mercury compounds on TRXR activity has been demonstrated in vitro. In addition, mercuric chloride was estimated to be a more potent inhibitor of the enzyme when compared to methylmercury (Carvalho et al. 2008, 2010). These observations correspond to the results obtained during the investigation of mercury's influence on human monocytes (Wataha et al. 2008). It has been also shown that peroral methylmercury administration resulted in a significant decrease in murine liver and kidneys, but not in brain (Wagner et al. 2010). Moreover, the results obtained by Branco et al. have allowed the authors to propose that TRXR is one of the main targets of mercury toxic action (Branco et al. 2011). At the same time, an in vitro study using C2C12-DMPK160 cells has revealed positive regulation of TRXR activity by mercury treatment (Usuki et al. 2011).

Mercury and endoplasmic reticulum stress

The high affinity of mercury to protein sulfhydryl groups can lead to the accumulation of degenerated proteins accompanied by the development of the ERS (Usuki et al. 2008).

The results of excellent research by Sharma et al. have shown that mercury inhibits the protein folding and the degree of inhibition is directly correlated to its the reactivity with thiol, imidazole, and carboxyl groups (Sharma et al. 2008). It should be noted that in this study, mercury had a more pronounced effect compared with Cd and Pb being inducers of ERS (Kitamura and Hiramatsu 2010; Qian and Tiffany-Castiglioni 2003).

Numerous in vitro studies using various cell cultures have demonstrated the possibility of mercury-induced ERS. In particular, it has been shown that the presence of mercuric chloride in the incubation medium in concentrations of 0.1 and 1 μM caused an increase the GRP78 mRNA levels, and time-and dose-dependent elevation of cellular GRP78 levels (Qian et al. 2001) that is supposed to be a marker of unfolded protein response (Lee 2005). Real-time quantitative PCR has revealed more than 2-fold induction of GRP78 mRNA expression after 9 h of incubation C2C12-DMPK160 and C2C12-DMPK5 cells in the presence of mercury, indicating the development of ERS at the later stages of methylmercury toxicity (Usuki et al. 2008). The effect of mercuric chloride on cell line NRK-52E has resulted in a marked activation of the HSP72 expression (Stacchiotti et al. 2009a, b), being a stress-inducible protein and critical regulator of ERS (Liu et al. 2010). The prevention of methylmercury toxic action in myogenic cell line through ER stress modulation using an inhibitor of endoplasmic Ca-ATPase (thapsigargin) also supports the hypothesis of the involvement of ERS in mercury toxicity (Usuki et al. 2013). Exposure to methylmercury in the fetal rat central neural system (CNS) cells have also resulted in a significant increase in the Gadd153 expression (Ou et al. 1997; Faustman et al. 2002), that is along with GRP78 considered to be a key indicator of ERS (Liu et al. 2010). Similar changes have also been observed in the brain of rats prenatally exposed to methylmercury (Faustman et al. 2002). Intraperitoneal injections of methylmercury in rats have resulted in a significant increase in GRP78 both at protein and mRNA levels in cerebral cortex (Zhang et al. 2010, 2013). Induction of HSP72 and GRP78 expression was also detected in the liver of Wistar rats, receiving mercuric chloride in a concentration of 0.1 mg/kg for 3 days (Stacchiotti et al. 2009a, b). Moreover, a number of morphological studies using different cell lines have revealed the mercury-induced dilation of the rough ER (Goering et al. 1999; Carranza-Rosales et al. 2005), which also may indicate the development of ERS (He and Liang 2013).

Mercury and inflammation

Like many other metals, mercury is postulated to be an inductor of inflammatory response. Investigation of miners has indicated that occupational exposure to mercury results in a significant increase in serum

proinflammatory cytokines: interleukine (IL)-1β, tumor necrosis factor α (TNFα), and interferon-γ (IFN-γ). At the same time, mercury-associated increase in antinucleolar antibodies' levels has been noted (Gardner et al. 2010a, b). A later study has revealed elevated titers of antinuclear, but not antinucleolar antibodies in methylmercury-exposed Brazilians. Moreover, a significant association between serum IL-4, IL-6, IL-17 and IFN-γ levels and different markers of organisms' mercury content has been found (Nyland et al. 2011). The study involving children consuming different amounts of fish have demonstrated a correlation between blood serum mercury levels and acute-phase proteins (Gump et al. 2012). On the contrary, no significant association between blood mercury and cytokines has been revealed in the investigation of children and women (Nyland et al. 2011).

Animal studies partially confirm the clinic-epidemiologic data. Particularly, peroral administration of mercuric chloride resulted in a dose-dependent increase in liver TNFα, IL-2 and IFN-γ expression. However, no significant influence on IL-1 and IL-4 has been observed. Similar changes were detected in renal tissue, whereas the change in cytokine expression in spleen and thymus was multidirectional, being characterized by partial decrease (Kim et al. 2003). Further studies have shown that mercury administration results in activated expression of TNFα in livers of intact and lipopolysaccharide (LPS)-treated animals. It is supposed that the observed effect is mediated through p38 mitogen-activated protein kinase (MAPK) signaling (Kim and Sharma 2005). It has been also estimated that intraperitoneal injection of mercuric chloride increases serum TNFα levels in rats (Tunali-Akbay et al. 2007). Another study using peroral administration of mercury has noted a significant increase in urinary IL-1β levels, whereas the changes in TNFα and IL-6 concentrations were less expressed (Rumbeiha et al. 1998). A detailed study by Liu and colleagues has estimated that mercury vapor inhalation increases the expression of TNFα, TNF-receptor-1, IL-2 and IL-7 in rat lungs (Liu et al. 2003).

Cell culture studies have also indicated the involvement of mercury in the development of inflammatory reaction. Specifically, peripheral blood mononuclear cells were characterized by a significantly increased IL-1β and TNFα secretion and decreased anti-inflammatory cytokine production in response to mercuric chloride treatment. It is also notable that production of IL-4, IL-17 and IFN-γ increased along with elevation of mercury concentrations (Gardner et al. 2009). Further investigations have indicated that incubation of peripheral blood mononuclear cells in the presence of mercuric chloride resulted in a dose-dependent increase in TNFα production. HgCl2 also increased the level of IL-1β, IL-17 and TNFα in the presence of LPS in the medium. At the same time, a significant stimulatory action of methylmercury was observed only in the case of IL-1β. It is remarkable that ethylmercury treatment has resulted in decreased levels of IFN-γ, IL-1β and TNFα in the cell culture under LPS-mediated stimulation (Gardner et al. 2010a, b). Another study using peripheral blood mononuclear cells has shown an increase in TNFα, IL-1β, IL-6 and IL-8, but not IL-10 production in response to 1–5 μM HgCl2. Moreover, further increase in mercury concentration (up to 10 μM) caused a significant inhibition of the abovementioned cytokines' production in comparison to the control values (Villanueva et al. 2000). An investigation of mercury's influence on peripheral blood mononuclear cells obtained from healthy donors and stimulated with monoclonal antibodies obtained opposite results. In particular, treatment of cells with mercuric chloride resulted in decreased TNFα, IL-6 and IFN-γ production. However, the cells from three donors were characterized by an increase in cytokine production. Similar results have been received in cells activated by heat-killed Salmonella enterica (Hemdan et al. 2007). A stimulatory effect of mercury on IL-4 production by peripheral blood mononuclear cells has also been marked. It is also notable that methylmercury had more impact on cytokine production when compared to inorganic mercury (De Vos et al. 2004; de Vos et al. 2007).

The interaction between mercury exposure and inflammation has also been described in a number of animal cell cultures. Thus, the ability of mercuric chloride to induce IL-1 secretion in macrophages obtained from different murine strains has been demonstrated (Zdolsek et al. 1994). Moreover, later study allowed to suppose that IL-1 plays the leading role in regulation of mercury-induced proliferation of T-lymphocytes (Pollard and Landberg 2001). Preincubation of cultivated lymphocytes from Hg-susceptible and Hg-resistant mice in a mercury-containing medium was followed by activation of cell proliferation and increase in IFN-γ and IL-2 secretion (Hu et al. 1997). Mast cells

have also been characterized by a significant increase production of IL-4 in response to mercuric chloride (Wu et al. 2001). Presumably, this effect may be mediated via c-Jun-N-terminal kinase signaling (Walczak-Drzewiecka et al. 2005). These results are in agreement with earlier indications of mercury-induced degranulation and TNFα and IL-4 secretion by mast cells (Dastych et al. 1999). Moreover, a recent study demonstrated a stimulation of IL-6 and vascular endothelial growth factor (VEGF) release from mercury-treated mast cells (Kempuraj et al. 2010). An exploration of different mercury concentrations' effect on LPS-stimulated macrophages has shown that metal treatment significantly increased TNFα production and potentiated LPS-induced expression of TNFα and IL-6 mRNA. This alteration was associated with a dose-dependent decrease in $NO^{\bullet}$ production and inhibition of inducible NO-synthase mRNA expression. The authors suppose that these changes are interrelated with the observed activation of p38-MAPK signaling (Kim et al. 2002). Moreover, mercury has been shown to activate NF-kB (Park and Youn 2013), being the key regulator of inflammatory response (Baldwin 1996).

At the same time, indications of the inhibitory action of mercury compounds on TNFα and IL-1 synthesis are also present (Zefferino et al. 2006).

Impact of mercury on the development of metabolic syndrome components

Mercury, dyslipidemia and atherosclerosis

Multiple studies have obtained contradictory data regarding interrelation between mercury exposure and atherosclerosis development. In particular, a population-based prospective 4-year follow-up study among 1,014 men demonstrated a significant association between hair mercury levels and carotid intima-media thickness. Moreover, the results have indicated that for every 1 μg/g of hair mercury content, there was on the average an increment of 8 mm in the 4-year increase in the common carotid intima-media thickness (Salonen et al. 2000). An extensive study involving 33,737 persons have not confirmed the interrelation between mercury exposure and the incidence of coronary artery disease (Yoshizawa et al. 2002). Similarly, the analysis of heavy metal urine concentration in persons suffering from coronary heart disease failed to reveal a significant association between urinary mercury levels and severity of the disease (Sponder et al. 2014).

More consistent data were obtained during the analysis of relationship between mercury exposure and dyslipidemia. Thus, a significant association between the amount of mercury consumed and serum low-density lipoprotein cholesterol (LDL-C) has been estimated. Moreover, a strong negative correlation between mercury consumption and high-density lipoprotein cholesterol (HDL-C) has been revealed (Meltzer et al. 1994). An investigation of 477 Koreans has also indicated a significant interrelation between blood mercury and LDL-C and HDL-C levels (You et al. 2011). It has been demonstrated that mercury levels correlate with serum TG and HDL-C in a group of smokers. A significant interrelation has been estimated between blood Hg and LDL-C concentrations (Hong et al. 2013). Our previous studies have also shown a significant association between hair mercury levels and serum TG (Tinkov et al. 2014). Another study has shown that hair mercury levels are directly interrelated with serum total cholesterol, TG and LDL-C concentrations, whereas HDL-C was characterized by an inverse correlation with hair metal levels (Lim et al. 2008).

The influence of mercury on paraoxonase, a HDL-associated enzyme (Mackness and Mackness 2004), has been characterized by previous studies. In particular, an investigation of 896 Inuit adults from Nunavik has shown that blood mercury levels are associated with paraoxonase 1 activity (Ayotte et al. 2011). Similar data have been obtained by other researchers (Pollack et al. 2014; Drescher et al. 2014).

Experimental studies have at least partially confirmed clinic-epidemiologic data. Thus, subcutaneous injection of 5 mg/kg mercuric chloride during 60 days resulted in a nearly 3-fold increase in TG and LDL-C levels and a 30 % decrease in serum HDL-C. A 25 % increase in total cholesterol in relation to the control values was also observed (Bashandy et al. 2011). Moreover, 20 mg/l methylmercury administration to mice of different strains for 21 day has induced a significant increase in serum total cholesterol and non-HDL cholesterol (Moreira et al. 2012). Intraperitoneal injection of 5–10 mg/kg methylmercury has resulted in a significant elevation of serum TG, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and hepatocyte TG. These changes were accompanied by a

decrease in serum HDL-C (Taher et al. 2000). At the same time, an investigation using peroral administration of 0.25 mg/kg HgCl2 for 30 days has indicated a decrease in serum total cholesterol and TG concentrations in comparison to the control values (Merzoug et al. 2009). It has been also shown that mercuric chloride induced a 28 % decrease in paraoxonase 1 activity and an increase in susceptibility of LDL to oxidation (Jaiswal and Rizvi 2013).

Mercury and hypertension

Multiple indications of mercury exposure and its content in the organism and hypertension development exist. In particular, an investigation of 101 Wisconsin Sleep Cohort Study participants has shown that elevated blood mercury is associated with 1.9-fold increase in hypertension risk. It is also notable that no interrelation between mercury levels and vascular reactivity has been revealed (Bautista et al. 2009). A number of studies has noted an association between the content of mercury in different biosubstrates and the values of systolic (Valera et al. 2009), diastolic (Fillion et al. 2006; Lim et al. 2008; Hong et al. 2013), and pulse blood pressure (Pedersen et al. 2005).

The KNHANES IV and V (2008-2009; 2010) studies involving 6,213 persons (3,060 men and 3,153 women) have indicated a significant association between serum ferritin, mercury and the incidence of hypertension. In this connection the authors suppose that the simultaneous increase in serum ferritin and mercury levels may be indicative of higher hypertension risk (Choi et al. 2013). A two-year NHANES IV (1999–2000) observation has also shown a significant interrelation between blood mercury and blood pressure. Moreover, is has been noted that for every 1.3 μg/l increase in mercury, systolic blood pressure significantly increased by 1.83 mm Hg (Vupputuri et al. 2005).

At the same time, the question of interrelation between mercury and hypertension has a number of controversies. Particularly, the comparison of hypertension risk in two prospective cohorts has not revealed a significant impact of organism's mercury levels on hypertension development. Moreover, even a 2.5-fold increase in toenail mercury in comparison to the reference ranges was not associated with higher hypertension risk (Mozaffarian et al. 2012). The NHANES 2003-2006 investigation of 6607 men also has failed to observe a significant association between blood mercury levels and hypertension (Park et al. 2013).

Clinical observations indicate an association between mercury exposure and hypertension. Wössmann and colleagues have observed a 11-year old girl with mercury-induced hypertension and tachycardia (Wössmann et al. 1999). Hypertension and tachycardia have also been revealed in a 4-year boy and his 6-year sister. Chelation and antihypertensive therapy have resulted in a decrease in organism's mercury content and blood pressure normalization. The observed activation of renin-angiotensin aldosterone system (RAAS), as assessed by serum renin measurement, may serve as possible mechanism of mercury-induced hypertension (Torres et al. 2000).

Experimental studies also provide evidence of mercury's influence on hypertension. An investigation of alimentary mercury administration in different doses (1–30 μg/g of food) during 12 weeks has indicated a significant increase in blood pressure in spontaneously hypertensive rats. The authors assume that the observed elevation of blood pressure may be a consequence of atherosclerosis development (Takahashi et al. 2000). Intravenous injection of $HgCl_2$ (5 mg/kg) was followed by a decrease in left ventricle systolic pressure only after 40 min, whereas right ventricle systolic pressure increased. Both right and left diastolic pressures increased indicating a state of diastolic ventricular dysfunction. Moreover, perfusion of lungs with mercury-containing Krebs solution resulted in a 2-fold increase in pulmonary blood pressure (Rossoni et al. 1999).

An analysis of mercury's effect on pressor reactivity to phenylephrine in experimental animals has also been carried out. It has been shown that low doses of mercury increase sensitivity and maximal response to phenylephrine pressor reactivity. Moreover, a $HgCl_2$-induced elevation in basal systolic, diastolic blood pressure, and heart rate has been demonstrated in rats (Machado et al. 2007).

To specify the mechanisms of mercury's influence on blood pressure, a number of investigations using cell cultures and isolated animal tissues have been carried out. It has been demonstrated that mercury-induced vascular reactivity to phenylephrine is mediated by cyclooxygenase (COX) 2 activation and subsequent synthesis of vasoconstrictor prostanoids. The authors have also shown that the activation of RAAS may take place in the realization of the

observed effect, as estimated by the absence of phenylephrine-induced vascular contraction after the use of angiotensin 1 receptor inhibitor (Pecanha et al. 2010). These results are in agreement with earlier data from the investigation of the rat tail vascular reactivity (da Cunha et al. 2000).

Treatment with mercury-containing Krebs-Henseleit solution has caused a contraction of rabbit aortic segments in vitro. The removal of Ca2+ ions from the buffer or a decrease in pH reversed the observed effect, being indicative of the significant role of calcium in mercury-induced contraction (Tomera and Harakal 1986). However, opposite results indicating an inhibition of Taenia coli smooth muscle contraction after mercury treatment (0.005–0.5 mM) have been obtained. The authors suppose that this effect is mediated through mercury-induced inhibition of calcium transport into the cell (Nasu et al. 1984).

Smooth muscle contraction in response to mercury treatment has also been indicated in kidneys of anesthetized dogs and in rabbit aortic strips. Alpha-adrenergic blockade reversed the effect, being indicative of the role of catecholamine release in the mercury-induced contraction (Solomon and Hollenberg 1975).

The influence of mercury on vascular smooth muscle cells has been investigated in an experiment using Wistar rats injected with mercuric chloride for 30 days. Particularly, mercury induced vascular wall remodeling characterized by activation of smooth muscle cell proliferation. Activation of NADPH-oxidase (both at gene and protein levels), COX2, extracellular-signal-regulated kinases (ERK) 1/2, and p38 signaling has been proposed as a possible mechanism of the observed effect. In addition, the use of specific inhibitors has indicated that mercury-induced activation of NADPH-oxidase and COX2 are mediated through proinflammatory MAPK pathway signaling (Aguado et al. 2013). The respective results have been received in an experiment studying the effect of apocynin, a NADPH-oxidase inhibitor, on mercury-induced endothelial dysfunction. Briefly, the intramuscular injection of mercuric chloride has resulted in increased aorta reactivity to phenylephrine and decreased endothelial reaction to acetylcholine. Along with vasoconstriction an increase in ROS and vasoconstrictor prostanoid production on a background of decreased SOD and GPx activity has been observed. The decrease in NO production in mercury-treated animals has also been detected. Administration of apocynin partially decreased vascular reactivity to phenylephrine and restored the level of NO and the realization of NO-dependent effects. However, the level of vasoconstrictor prostanoids in apocynin-treated animals was not altered (Rizzetti et al. 2013).

A number of other observations also confirm the role of NAPDH-oxidase in mercury-induced vasoconstriction. Particularly, the preincubation of left coronary arteries in the mercuric chloride-containing medium has resulted in increased serotonin-induced vasoconstriction and inhibition of acetylcholine-induced vasorelaxation. A decrease in nitric oxide production, activation of superoxide production and increase in NADPH-oxidase subunits' mRNA expression has also been observed. Tyron, a superoxide scavenger, prevented excessive serotonin-induced vasoconstriction and restored the vasorelaxative action of acetylcholine (Furieri et al. 2011).

Along with the role of oxidative stress in vascular smooth muscle cell contraction, oxidative stress-mediated mercury-induced endothelial dysfunction has also been demonstrated. High metal concentrations (>3–5 μM) possessed cytotoxic activity, whereas low mercury concentrations (<1–2 μM) have stimulated glutathione synthesis, being indicative of defensive mechanisms' induction (Wolf and Baynes 2007).

Mercury treatment has also been accompanied by activation of phenylephrine vasoconstrictory action and inhibition of vasorelaxative action of acetylcholine in rats' aorta and mesenteric resistance arteries, being indicative from the authors' view of impaired NO production. Basal systolic blood pressure has not changed. Intensified ROS production is proposed to be a possible mechanism of mercury-induced endothelial dysfunction. This hypothesis may be confirmed by the evidence of decreased reactivity to phenylephrine and restoration of acetylcholine-induced vasorelaxation in vessels from mercury-exposed rats being treated with SOD and apocynin (Wiggers et al. 2008a, b).

It is also notable that L-arginine supplementation in mercury-treated mice has resulted in decreased mercury accumulation in thymus and increased NO-synthase activity (Bracci et al. 2008). Despite these results have been obtained on a tissue that does not have direct influence on hemodynamics, the observed effect may indicate antagonistic relationship between mercury and NO in the organism.

However, data showing the opposite effect of mercury on NO production exist. In particular, one of the investigations has shown that peroral administration of mercury results in increased vasorelaxative effect of acetylcholine on aorta. At the same time, the researchers have noted an increase in NO-synthase activity and oxidative stress development (Omanwar et al. 2013). Interesting data have been obtained in an investigation of mercury's influence on norepinephrine preconstricted rat aorta and pulmonary artery rings. Incubation of the vessels in mercury-containing medium resulted in endothelium-dependent vasorelaxation that has been totally blocked by the nitric oxide inhibitor NG-nitro-L-arginine methyl ester (L-NAME). Along with vasorelaxation, HgCl2 treatment has been accompanied by functional and morphological alterations of the endothelial cells (Golpon et al. 2003).

The involvement of RAAS activation in mercury-induced hemodynamic changes has been confirmed by the observations of inhibitory action of enalaprilate on Hg-induced vascular reactivity. It has also been estimated that mercury increases angiotensin converting enzyme activity (Wiggers et al. 2008a, b).

Moreover, N. L. Parinandi and coauthors have estimated that mercury activated phospholipase D in bovine pulmonary artery endothelial cells. Calcium chelating agents and decreased calcium concentration in the incubation medium significantly reduce the observed effect of mercury. These data have allowed the authors to propose the role of calcium in mercury-induced activation of phospholipase D (Peltz et al. 2009). These researchers have also shown that the level of total cellular thiols and oxidative stress are the signaling mediators of mercury-induced activation of the enzyme (Hagele et al. 2007). Moreover, mercuric sulfate treatment has been shown to be accompanied by a dose- and time-dependent activation of phospholipase A_2 and subsequent synthesis of proinflammatory arachidonic acid metabolites. The role of mercury-induced phospholipase A_2 activation in endothelial dysfunction has also been demonstrated. It is notable, that these changes have been reversed by phospholipase A_2 inhibitor (Mazerik et al. 2007).

Hence, based on the results of clinic-epidemiologic and experimental studies it can be proposed that mercury promotes an increase in blood pressure. The scheme of possible mechanisms involved in mercury-induced hypertension is presented in Fig. 2.

Mercury and obesity

The KNHANES IV (2008–2009) results have shown that blood mercury levels are significantly interrelated with overweight and obesity (Cho et al. 2014). Moreover, an investigation involving 1,853 persons in KNHANES 2010 has demonstrated an association between blood Hg and BMI and waist circumference values. A non-significant interrelation between mercury levels and adipose tissue contents has also been detected (Kang and Lee 2013). Our previous data have indicated that obese and overweight persons are characterized by higher hair mercury levels (Skalnaya et al. 2014). Moreover, an investigation of persons aged from 5 to 69 years has revealed a significant correlation of hair mercury content, age and body weight (Skalnaya et al. 2014, unpublished data). In persons being exposed to mercury and dioxins a significant association between serum mercury and waist circumference has been noted (Chang et al. 2011). In addition, an observation involving 477 Koreans living in coastal area has demonstrated a significant statistical interaction between blood mercury levels and waist-to-hip ratio (You et al. 2011).

However, recent study has shown an inverse association between organisms' adipose tissue content and blood mercury levels (Park and Lee 2013).

In spite of large clinic-epidemiologic data indicating an association between mercury exposure and obesity, experimental data are insufficient.

A recent in vivo investigation has demonstrated that mercuric chloride administration in mice was followed by a decrease in adipose tissue content, as well as decreased adipocyte size and leptin secretion. At the same time, a significant inhibition of both peroxisome proliferator-activated receptor (PPAR)α and PPARγ mRNA expression in adipocytes has been indicated. Despite a significant mercury-induced decrease in adipose tissue content, the authors suppose that the observed changes may play an important role in the development of obesity associated-pathology (Kawakami et al. 2012).

Mercury and insulin resistance

Multiple studies have demonstrated the influence of mercury on insulin resistance and type 2 diabetes mellitus (DM2) development. Particularly, the results of the Coronary Artery Risk Development in Young

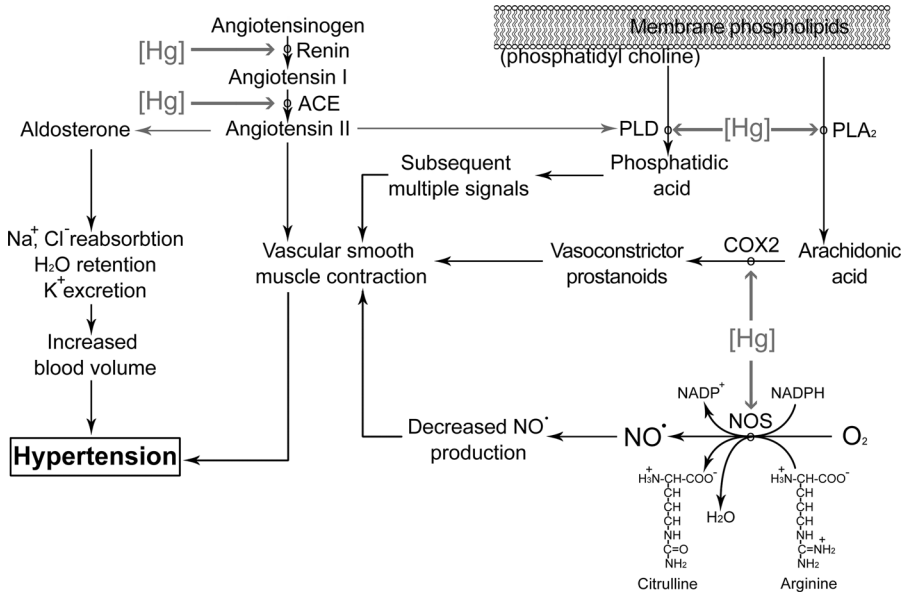

Fig. 2 A hypothetic scheme of mercury's influence on hypertension pathogenesis. Activation of RAAS occurs via positive influence of mercury on renin and angiotensin converting enzyme activity. The formed angiotensin II induces vascular smooth muscle cell contraction and aldosterone synthesis. The latter increases sodium and chloride reabsorbtion as well as water retention resulting in elevated volume of blood circulation. Mercury-induced inhibition of NO-synthase results in decreased NO levels and consequently to impaired vasorelaxation and increased vasculature contraction. Possible mercury-induced phospholipase A2 and COX2 activation causes increased production of vasoconstrictory prostanoids and vascular smooth muscle cell contraction. Activation of phospholipase D under the influence of both mercury and angiotensin II results in increased phosphatidic acid production. The latter is supposed to take part in multiple signaling pathways leading to vasculature contraction

Adults (CARDIA) Trace Element Study involving 3,875 Americans have shown that toenail mercury content is positively associated with DM2 incidence (He et al. 2013). It has been also demonstrated that mercury exposure in related to decreased homeostasis model assessment of β-cell function index (He et al. 2013). Chemical analysis has shown that diabetic patients are characterized by higher serum mercury values. Moreover, a tendency to an increase in urine mercury has also been observed (Flores et al. 2011). Type 2 diabetic persons were also characterized by higher hair mercury values in comparison to the control group (Nakagawa 1995). Our earlier data have indicated a nearly 2fold increase in hair mercury levels in diabetic persons when compared to the control group of healthy people (Skalnaya and Demidov 2007). A near significantly higher hair mercury content has been observed in Ontario inhabitants suffering from DM2 in comparison to the control group (Pal et al. 2013). Moreover, in a cohort simultaneously exposed to dioxins and mercury an increase in insulin resistance was associated with elevation of blood serum mercury concentrations (Chang et al. 2011).

However, a number of contradictions in the question exist. In particular, KNHANES results have demonstrated that serum mercury is not significantly associated with diabetes incidence in the population (Moon, 2013). Moreover, habitation in the high-mercury areas has been not followed by an increase in DM2 frequency (Futatsuka et al. 1996). At that, a systematic analysis of data indicating an association between diabetes and environmental chemicals has underlined the necessity of additional prospective studies (Kuo et al. 2013).

Experimental in vivo studies regarding the influence of mercury compounds on diabetes development are also contradictory. It has been shown that subcutaneous injection of mercury in different periods (5, 10, 21 days) is followed by the suppression of insulin resistance and delayed onset of diabetes in non-obese diabetic (NOD) mice (Brenden et al. 2001). Another

investigation has indicated that peroral administration of mercuric chloride and methylmercury is accompanied by a decrease in serum insulin levels, hyperglycaemia, glucose intolerance and an increase in serum TBARS concentration. The observed changes have been reversed by *N*-acetylcysteine administration, being indicative of the role of oxidative stress in mercury-induced glucose dyshomeostasis (Chen et al. 2006a, b, c, d).

Cell culture studies have indicated that mercuric chloride treatment decreased insulin secretion and increased ROS formation and subsequent cell damage in a dose-dependent manner. At that, mercury treatment has increased the percent of both apoptotic and necrotic cells. The observed effects have also been reversed by *N*-acetylcysteine treatment (Chen et al. 2010). Similar results have been obtained in the study of mercury's influence on β-cell function (Chen et al. 2006a, b, c, d).

It has been also shown that methylmercury dose-dependently decreases insulin-mediated glucose uptake by murine skeletal muscles. Moreover, mercury-dependent inhibition of insulin-induced Akt phosphorylation has been noted. The observed effects have been also reversed by *N*-acetylcysteine treatment (Ibrahim 2011). In the excellent work by Chen and coauthors it has been demonstrated that mercury-induced oxidative stress and phosphoinositol-3-kinase activation caused β-cell dysfunction, that is associated with Akt signaling. It is notable that these effects have been observed both after mercuric chloride and methylmercury treatment (Chen et al. 2006a, b, c, d).

It is notable that single observations indicate a positive influence of mercury on glucose metabolism. Particularly, it has been demonstrated that mercuric ions stimulate adipocyte glucose uptake due to translocation of glucose transporter from cytoplasm to membrane. These results have allowed the researchers to propose insulin-mimetic action of mercuric ions by a post-receptor/kinase mechanism in vitro (Ezaki 1989). Further studies have partially confirmed and specified these data. Mercury treatment increased adipocyte glucose uptake (1.8-fold in comparison to insulin). However, this elevation was mediated by glucose transporter 1 (GluT1), not by GluT4. Mercury treatment also resulted in an increase in p38 kinase phosphorylation, being indicative of adipocyte stress reaction that may play a significant role in insulin resistance. It is also notable that preincubation of adipocytes in mercury-containing medium inhibited insulin-mediated glucose transport, also being indicative of the role of mercury in insulin resistance development (Barnes and Kircher 2005). The investigation using two adipocyte cell lines has demonstrated that mercury treatment decreased adipocyte lipid content and PPARγ expression. 10T1/2 cells responded to mercury exposure by a decrease in GluT4. It is also notable that mercury-induced increase in basal glucose uptake was accompanied by a significant decrease in insulin-mediated glucose uptake. These changes were associated with increased JNK phosphorylation in 10T1/2 cells, whereas 3T3-L1 adipocytes were not characterized by this alteration. The obtained data are also indicative of the mercury's role in insulin resistance (Barnes et al. 2003). Human liver carcinoma cells' study has estimated that mercury treatment is followed by altered expression of genes taking part in p38 MAPK and PPAR signaling that regulate insulin's metabolic effects (Ayensu and Tchounwou 2006).

Complex organic mercury compounds have also shown to alter glucose homeostasis. Earlier studies on β-cells obtained from obese and hyperglycemic mice have estimated that organic mercurials (p-chloromercuribenzoic acid and chloromercuribenzene-p-sulphonic acid) stimulate insulin secretion. However, at higher concentrations these compounds have inhibited glucose transport and increased mannitol and sucrose spaces of isolated islets (Bloom et al. 1972). Treatment of adipocytes with mercuric ions and p-chloromercuriphenylsulfonate inhibited insulin-stimulated cellular glucose uptake without affecting antilipolytic action of the hormone. Moreover, organic mercury decreased adrenaline-mediated stimulation of glucose catabolism in adipocytes (George 1971).

In vitro studies have also indicated that mercuric chloride induces pancreatic β-cell depolarization. The latter leads to an increase in intracellular calcium concentrations due to its release from endoplasmic reticulum (Liu and Lin-Shiau 2002).

Conclusion

The above mentioned data undoubtedly indicate the impact of mercury on oxidative stress, ERS and inflammation. This type of action allows for a significant influence of mercury compounds on MetS

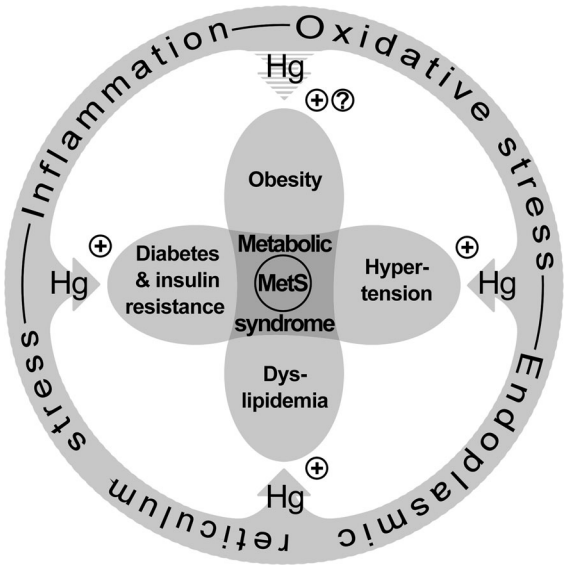

Fig. 3 Hypothetical scheme of the involvement of mercury in the development of metabolic syndrome and its components. In particular, mercury-induced oxidative stress, endoplasmic reticulum stress and inflammation lead to the development of insulin resistance, hypertension and dyslipidemia that is confirmed by multiple clinic-epidemiologic and experimental data. At the same time, the role of mercury in obesity development seems unexplored

pathogenesis. Moreover, single studies indicating the association between mercury exposure and the incidence of MetS are in accordance with data on significant interrelation between Hg exposure and individual MetS components. At the same time it is important to note insufficient data regarding the cause-effect relations between mercury and obesity. In particular, multiple studies demonstrate an association between organism's mercury levels and BMI values. However, there is a lack of data indicating the interrelation between mercury exposure and the mechanisms of obesity pathogenesis. Despite this fact, the demonstrative base of the mercury's role in the development of other MetS components seems valuable. Thus, the complex hypothetic scheme of mercury's impact on MetS formation may be presented at Fig. 3.

Perspectives

The present state of data regarding the interrelation between mercury and MetS denotes the following perspectives:

(1) Further clinic-epidemiologic and experimental studies are required to estimate the association between mercury exposure and the development of MetS components, especially obesity.

(2) Additional investigations of the possible effect of organism's mercury content modulation on MetS pathogenesis should be undertaken.

Acknowledgments The authors would like to thank Prof. Richard A. Anderson for helpful discussions and corrections of the manuscript. The current research is supported by Russian Ministry of Education and Science within project No. 2014/258-544.

Conflict of interest The authors declare no conflict of interest.

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