Kidney and Heavy Metal Exposure

Subjects: Toxicology

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Mitochondrial injuries appear to be an important factor in cellular senescence. The free radical theory of aging states that generation and leakage of ROS (reactive oxygen species) from the mitochondrial respiratory chain increases with age and leads to intracellular oxidative damage. Deterioration of mitochondrial DNA will impair the function of the respiratory chain, which is accompanied by additional ROS formation and DNA injuries. These events are hypothesized to involve a continuous cycle of reactive radical formation that may lead to accelerated aging.

Keywords: renal disease ; aging ; mercury ; cadmium ; lead ; thiols ; selenium

1. Overview

The aging process in the kidneys has been well studied. It is known that the glomerular filtration rate (GFR) declines with age in subjects older than 50–60 years. However, there is still insufficient knowledge regarding the response of the aged kidney to environmental toxicants such as mercury, cadmium, and lead. Here, we present a review on the functional decline and proposed mechanisms in the aging kidney as influenced by metal pollutants. Due to the prevalence of these toxicants in the environment, human exposure is nearly unavoidable. Further, it is well known that acute and chronic exposures to toxic metals may be detrimental to kidneys of normal adults, thus it may be hypothesized that exposure of individuals with reduced GFR will result in additional reductions in renal function. Individuals with compromised renal function, either from aging or from a combination of aging and disease, may be particularly susceptible to environmental toxicants. The available data appear to show an association between exposure to mercury, cadmium and/or lead and an increase in incidence and severity of renal disease in elderly individuals. Furthermore, some physiological thiols, as well as adequate selenium status, appear to exert a protective action. Further studies providing improved insight into the mechanisms by which nephrotoxic metals are handled by aging kidneys, as well as possibilities of therapeutic protection, are of utmost importance.

2. Mitochondrial Injuries

The kidney appears to be a major site of age-related changes, in addition to being a target for many environmental pollutants [1]. Long-term exposure to heavy metals such as mercury, lead, and cadmium may accelerate age-related renal deteriorations, which in part can be ascribed to the tendency of the accumulation of heavy metals in the kidneys during the processing of primary urine. Due to the increased life expectancy of humans living in the modern world, together with an increasing level of environmental metal pollutants with long elimination half-lives, it is likely that older individuals today accumulate higher levels of such toxic agents than individuals did some decades ago. Furthermore, the number of older individuals is increasing. Globally, more than 10% of the population are over the age of 60, and this percentage is predicated to rise substantially by 2050 [2]. A thorough understanding of the impact of age on various organs, including on the kidneys, is crucial when managing general healthcare, since elderly individuals make up a significant fraction of healthcare patients.

Numerous physiological changes occur in the aging kidneys, especially after the age of 70. Although healthy elderly individuals appear to be capable of maintaining normal renal function in spite of significant structural and physiological changes, this is achieved at the cost of the renal functional reserve. However, when the functional reserve is lost, kidneys have a reduced capacity to respond to external challenges, involving reduced ability to eliminate toxicants. Thus, old individuals may be more susceptible than younger ones when exposed to toxic metals from the environment.

The aging process results in numerous changes at the cellular and molecular levels. One of these changes involves a decreased ability to repair injured cells [3]. Concomitantly, acute phase reactants such as, e.g., C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) are expressed at higher levels [4].

Mitochondrial injuries appear to be an important factor in cellular senescence. The free radical theory of aging [5] states that generation and leakage of ROS (reactive oxygen species) from the mitochondrial respiratory chain increases with age and leads to intracellular oxidative damage. Deterioration of mitochondrial DNA will impair the function of the respiratory chain, which is accompanied by additional ROS formation and DNA injuries. These events are hypothesized to involve a continuous cycle of reactive radical formation that may lead to accelerated aging [6]. Several studies have indicated that aging is related to a declining expression of various anti-oxidative stress-related enzymes such as the superoxide dismutases (SOD1 and SOD2), catalase, and the glutathione peroxidases (GPXs) [7]. A reduction in the activities of these protective enzymes may lead to a further increase in oxidative stress and cellular aging. Exposure to mercury, cadmium, or lead, even on a low-grade scale, is known to affect anti-oxidative enzyme systems [8][9] and may thus promote age-dependent organ changes, especially in the kidneys [10]. The aim of the present review is to discuss the renal toxicity of mercury, cadmium, and lead compounds in elderly subjects, and the possible protective role of sulfur and selenium compounds.

3. Mercury, Cadmium and Lead—Nephrotoxic Environmental Pollutants

Toxic metals are abundant in the general environment, and at even higher levels in some occupational settings, implying that human exposure to these metals is inevitable. The cumulated exposure in elderly individuals to these nephrotoxic pollutants may promote age-dependent progression of renal deterioration [11]. Due to their function as the major route of excretion from the body, kidneys in aged individuals are especially vulnerable to heavy metal toxicity [10], mostly to mercury (Hg), cadmium (Cd), and lead (Pb). As for mercury, even minor exposures from its use in dental amalgams, vaccines, eye drops, and in traditional folk medicines may give rise to nephrotoxic effects, which may be difficult to assess because effects usually arise months or years after a low or moderate exposure [12][13]. Mercury is known to significantly affect human biochemical processes by interfering with the complex redox machinery used to regulate cell survival and mitochondrial function [14]. Cells with increased oxidative stress, for instance due to an inflammatory reaction in an aged individual, are presumed to be more susceptible to Hg toxicity than healthy cells under controlled conditions. Mercury occurs in three main forms, viz. elemental mercury (Hg^0), organic mercury (e.g., CH_3Hg^+, here denoted MeHg), and inorganic mercury (Hg^{2+}, Hg^+), the latter forms often occurring as salts (e.g., $HgCl_2$) [15]. All these forms have effects on the kidneys [16]. While inorganic Hg compounds are well-known nephrotoxic agents, exposure to elemental mercury vapor or to organic mercury may also involve nephrotoxicity in addition to their neurotoxicity. Elemental mercury (Hg^0) is a heavy liquid at room temperature; it is highly volatile and at saturation at 25 °C one m^3 of air contains 20 mg of Hg^0 that can be rapidly absorbed upon inhalation [17]. After uptake, a part of Hg^0 is oxidized to the nephrotoxic Hg^{2+} form [18].

Epidemiological studies gave evidence of renal injury following not only acute but also chronic exposure to various forms of mercury [19][20]. The most severe nephropathy is induced following exposure to inorganic salts of Hg^{2+} [16][21]. Accumulation of mercury in proximal tubular cells has been found to exert negative effects on antioxidative enzymes [22]. Thus, long-term exposure to mercury has been reported to decrease renal expression of enzymes involved in protective actions such as NADPH-quinone oxidoreductase and glutathione S-transferase [23]. In experiments with healthy rats exposed to $HgCl_2$, renal levels of SOD, catalase, and glutathione (GSH) were lowered, indicating the oxidative effects of Hg^{2+} [24]. Apparently, many of the injurious cellular effects of long-term mercury exposure, even at low doses, are similar to those induced by aging.

As for cadmium (Cd), severe pollution with this metal was first recognized by its skeletal manifestation named the *itai-itai* disease in Japan [25]. A few decades later, experimental studies revealed the harmful consequences of Cd^{2+} involving severe damage and histological changes in the kidneys, along with renal dysfunction [25].

In the liver and other tissues, Cd^{2+} forms a complex with the low molecular weight protein metallothionein (MT), which can be transported to and filtered by glomeruli, followed by reabsorption into the proximal tubuli. Intracellularly, in tubular cells, the MT-complex releases free Cd^{2+} upon overloading, thus causing renal damage, ia. through perturbing calcium homeostasis, inducing oxidative stress, and downregulating mitochondrial enzymes [26][27]. The Cd^{2+}-induced damage to proximal tubuli, identified as a reabsorptive dysfunction, is manifested by a characteristic proteinuria that may include albumin, but otherwise is dominated by low molecular weight proteins of which β_2-microglobulin and *N*-acetyl-β-d-glucosaminidase are used as markers [28]. A health survey in Sweden of women around 60 years of age disclosed associations between low levels of urinary Cd (around 0.6 µg/L) and increased levels of *N*-acetyl-β-d-glucosaminidase in urine, and also the effects on GFR [29]. The effects of low-level Cd exposure on renal tubular function were also observed in a later study by Wallin et al. [30]. An increased susceptibility for patients with diabetes to develop tubular dysfunction upon low to moderate Cd^{2+} exposure has been observed [31]. Associations between cadmium exposure and arterial hypertension have also been reported [32].

Regarding compounds of lead (Pb), these pollutants are usually absorbed readily by the intestines as well as by lungs upon exposure. From the circulation, Pb^{2+} is distributed into different tissues and organs, including the liver and kidneys, where it may cause oxidative damage to cells, ia. by uncoupling the respiratory chain in mitochondria [33]. Different hypotheses have been forwarded to explain the kidney toxicity of Pb^{2+}. Due to ionic similarities, Pb^{2+} may dysregulate the calcium homeostasis. As a result, Ca^{2+} release from mitochondria is stimulated, accompanied by opening of the mitochondrial transitional pores, resulting in generation of reactive species and oxidative stress [34]. Among the renal cells, proximal tubuli appear to be particularly susceptible to Pb^{2+}-induced damage, and studies on primary cultures of rat proximal tubular cells conformed to the assumption that Pb^{2+} elevates cytosol Ca^{2+} at the expense of mitochondrial Ca^{2+} [35]. Epidemiological associations between lead exposure and arterial hypertension have been observed [36]. In a prospective study [37] the observed decline in renal function among middle-aged and elderly individuals appeared to depend both on lead stores and circulating lead, the decline in renal function being most pronounced among the individuals with diabetes or hypertension at inclusion. Another prospective study on a cohort with age at inclusion of almost 60 years and a follow-up period of 16 years revealed that even low-level lead exposure was associated with decreased kidney function [38].

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