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Review article

# Metals, autoimmunity, and neuroendocrinology: Is there a connection?

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ABSTRACT

It has been demonstrated that metals can induce autoimmunity. However, few studies have attempted to assess and elucidate the underlying mechanisms of action. Recent research has tried to evaluate the possible interactions of the immune system with metal ions, particularly with heavy metals. Research indicates that metals have the potential to induce or promote the development of autoimmunity in humans. Metal-induced inflammation may dysregulate the hypothalamic-pituitary-adrenal (HPA) axis and thus contribute to fatigue and other non-specific symptoms characterizing disorders related to autoimmune diseases. The toxic effects of several metals are also mediated through free radical formation, cell membrane disturbance, or enzyme inhibition. There are worldwide increases in environmental metal pollution. It is therefore critical that studies on the role of metals in autoimmunity, and neuroendocrine disorders, including effects on the developing immune system and brain and the genetic susceptibility are performed. These studies can lead to efficient preventive strategies and improved therapeutic approaches. In this review, we have retrieved and commented on studies that evaluated the effects of metal toxicity on immune and endocrine-related pathways. This review aims to increase awareness of metals as factors in the onset and progression of autoimmune and neuroendocrine disorders.

## 1. Introduction

Global development has created increased anthropogenic pollution of the environment (Spiegel, 2017; Kumar et al., 2019). Human exposure to contaminants and pollutants derived from various sources, including industry, exhausts, implants (such as joint replacements, orthopedic screws, silicone breast implants, and dental fillings), food additives (preservatives and food colorants), and also increasing use of drugs due to psychological stress, to name a few (Nriagu, 1996; Frigerio et al., 2011; Orru et al., 2017; Luo et al., 2019; Papadogeorgou et al., 2019; Rodríguez-Estival et al., 2019). Among these pollutants, metals in ionic, particulate, and nanoparticle form, can cause respiratory and cardiovascular diseases, dysfunctions in the reproductive and central nervous system, together with cancer genesis (Mudgal et al., 2010; Zoroddu et al., 2014a). Increased reactivity to metals has been found in several diseases, as reported in Table 1. In this context, dental amalgams containing mercury (Hg) still represent a significant concern in terms of environmental impact and for human health (Bengtsson and Hylander, 2017). In parallel, there has been an increasing prevalence of chronic disease (Halliwell and Gutteridge, 1990; Van Rensburg et al., 2001; Genuis, 2010; Fox and Sampalli, 2015; Bjørklund et al., 2019a). Insight into the etiology and pathogenesis of the conditions mentioned in Table 1 is gradually increasing. The complex interaction of mechanisms between the immune system and the neuroendocrine systems that contribute to the induction of autoimmune disorders are being explored (Colamatteo et al., 2019; Huang et al., 2019; Kahlenberg and Kang, 2020). Furthermore, infectious agents may, through immunomodulation, compromise the immune system and increase sensitivity to the effects of environmental pollutant agents. The synergistic effects of these factors may play a role in the observed increase of autoimmune disease in the developed world (Cojocaru and Chicoş, 2014). The immunological effects of subtoxic doses of a metal, e.g., dermatitis

*Abbreviations:* ANoA, anti-nucleolar antibodies; CNS, central nervous system; CFS, chronic fatigue syndrome; FDA, food and drugs administration; HLA, human lymphocyte antigen; HPA, hypothalamic-pituitary-adrenal; mAb, monoclonal antibodies; MCS, multiple chemical sensitivity; MHC, major histocompatibility complex; PNS, peripheral nervous system

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**Table 1**
Diseases in immunologically metal susceptible individuals.

| DISEASE | REFERENCES |
|---|---|
| Multiple sclerosis | (Stejskal et al., 2006; Sheykhansari et al., 2018) |
| Chronic fatigue syndrome | (Stejskal et al., 1994; Sterzl et al., 1999) |
| Rheumatoid arthritis | (Sterzl et al., 1999; Bjørklund et al., 2018) |
| Fibromyalgia | (Stejskal et al., 2013; Bjørklund et al., 2018) |
| Amyotrophic lateral sclerosis | (Redhe and Pleva, 1994; Sutedja et al., 2009) |
| Cardiovascular disease | (Virtanen et al., 2007; Alissa and Ferns, 2011; Manousek et al., 2016) |
| Lupus erythematosus | (Procházková et al., 2004; Bjørklund et al., 2018) |
| Oral lichen planus | (Stejskal et al., 1996; Muris et al., 2015) |
| Oral burning and itching | (Procházková et al., 2006; Stejskal et al., 2006) |
| Skin diseases | (Procházková et al., 2004; Ionescu, 2009) |
| Sjögren's syndrome | (Stejskal et al., 2015; Bjørklund et al., 2018) |
| Autoimmune thyroiditis | (Hybenova et al., 2010; Duntas, 2011) |

after nickel exposure, do not follow a classical dose-response curve. Minute concentrations of an allergen are sufficient to induce systemic reactions in sensitized rodents individuals (Rowley and Monestier, 2005). In susceptible animals, metal-induced inflammatory reactions in the brain or elsewhere can be triggered despite low concentrations detected in body fluids (Rowley and Monestier, 2005). The role of immunologically mediated inflammation, including neuroinflammation, is reasonably well established. Numerous studies are designed from a toxicological approach, including epidemiological studies and measurements of concentrations of metals in the environment, tissues, and/or body fluids (Kádár et al., 2006; Duramad et al., 2007; Fenga et al., 2017). However, increased knowledge about individual sensitivity based on genotype and phenotype variability, together with the use of biomarkers for diagnosis of individual sensitivity seems to provide solutions in the detailed elucidation of mechanisms (Ladeira and Viegas, 2016; Pedrete and Moreira, 2018; Bjørklund et al., 2020). In the case of metal pathology appearing as autoimmunity, we recommend future research includes longitudinal studies of metal-sensitive patients in addition to traditional case-control studies.

### *1.1. Metals and autoimmune disorders*

The usual environmental factors that are implicated in the development of autoimmune diseases include bacteria, viruses, and xenobiotics, such as chemicals, drugs, and metals. Many cases of autoimmunity are reported following an infection, for instance, after Epstein-Barr virus infection (Rachmawati et al., 2015; Stejskal, 2015). However, it seems that despite persistent research efforts, no conclusive evidence has linked particular microorganisms or viruses to the pathogenesis of specific autoimmune diseases. Several different factors have been studied concerning the induction of autoimmunity without a clear consensus (Guzzi et al., 2008; Zhang and Lawrence, 2016). The link between the human lymphocyte antigen (HLA) and susceptibility toward the development of autoimmune disorders has only a limited predictive value, thus indicating that other factors also contribute to the development of autoimmunity (Martin, 2004; Ooi et al., 2017). Clinical experience and scientific literature established that metals might play an important role in the development of autoimmune diseases. Humans are frequently sensitized to metals found in the environment or used in orthopedic implants, dentistry, food, vaccines, coins and jewelry (Table 2). More generally, a recent FDA Report on the Biological Responses to Metal Implants (FDA, 2019), showed that a wide variety of metals and metal alloys are used in dentistry, including platinum, gold, palladium, silver, ruthenium, iridium, osmium, and rhodium altogether with metal alloys including cobalt-chromium and nickel-chromium used in crowns, bridges, and partial dentures. Metals in dentistry also include nickel-titanium and cobalt chromium-nickel alloys, usually employed for orthodontic archwires, but also stainless steel alloys for preformed crowns and orthodontic brackets; or even titanium alloys for

**Table 2**
Major metals causing autoimmune disorders.

| METAL | TYPE OF STUDY | ACTION | REFERENCES |
|---|---|---|---|
| Molybdenum, Lithium | Case-control, cross-sectional study included 225 patients, 120 healthy controls, and 105 SLE patients | ↑ Increased levels in SLE patients | Pedro et al. (2019) |
| Molybdenum | Case report | ↑ Trigger for SLE | Federmann et al. (1994) |
| Beryllium | Review | ↑ Induction of autoimmunity | Fontenot (2018) |
| Vanadium, Zinc, Lead | Case-control, cross-sectional study included 225 patients, 120 healthy controls, and 105 SLE patients | ↓ Reduced levels in SLE patients | Pedro et al. (2019) |
| Nickel | Meta-analysis/Survey | ↑ Triggers autoimmune reactions of the skin | Drenovska et al. (2019) |
| Mercury | Review | ↑ Induction of autoimmunity | Pollard et al. (2019) |
| | Case report | ↑ Damage in cells involved in multiple sclerosis | Pamphlett and Kum Jew (2018) |
| | Case report | ↑ Membranous nephropathy | Onwuzuligbo et al. (2018) |
| Lead | Review | ↑ Elicits immune disorders leading to autoimmunity | (Fenga et al., 2017; Mishra, 2009) |
| Chromium | Metadata survey | ↑ Increase risk of Sjögren's syndrome | Lee et al. (2019) |
| Cadmium | In vitro assay | ↑ Immune modulation on popliteal lymph nodes causing autoimmunity | Carey et al. (2006) |
| Copper, Zinc | Case report | ↓ Reduced levels in scleroderma | Nishiyama and Miyawaki (2002) |
| Iron | An observational, multicentre, cross-sectional study | ↓ Reduced in autoimmune atrophic gastritis | Lenti et al. (2019) |
| Gold | Case report | ↑ Rheumatic autoimmune disorder | Möller et al. (1996) |
| Nickel, Gold, Aluminum, Mercury | Survey/Review | ↑ Triggering autoimmune disorders | Stejskal (2015) |
| Mercury, Cobalt, Chromium | Case report | ↑ ASIA | Stejskal (2013) |
| Nickel, Mercury, Gold, and Palladium | Study | ↑ Triggering autoimmune connective tissue disorders | Stejskal et al. (2015) |
| Nickel, Mercury, Tin, Silver, and Cadmium | Review | ↑ Triggering autoimmune thyroiditis | Hybenova et al. (2010) |
| Titanium | Case report | ↑ Delayed sensitivity | Müller and Valentine-Thon (2006); Evrard et al. (2010) |
| | Review | Triggering autoimmune disorders | |

endosseous implants and bone fixation plates and screws. Also, tungsten has a long implant history primarily because of its exceptional physical properties that have made its use attractive in several medical fields (orthopedics, vascular medicine, prosthodontics, and many others). However, numerous examples of tungsten-based medical device corrosion have been reported, resulting in the dissolution of tungsten and tungstate ions in the human physiological environment with consequent toxic and immunologic effects (Bolt and Mann, 2016; Shah Idil and Donaldson, 2018; Zoroddu et al., 2018).

HLA typing of metal-sensitive patients show higher frequencies of certain HLA antigens, among others HLA DR 4 and HLA B27. The former antigen is significantly increased in palladium-sensitive patients (Procházková et al., 2000). Chronic beryllium disease of the lungs (berylliosis) is associated with inhaling beryllium fumes, but inhaling beryllium does not always lead to chronic berylliosis. An exposed person usually becomes sensitized to beryllium before developing the disease. Sensitization is similar to an allergy; when allergic or sensitized, the body reacts negatively to that particular substance. Beryllium sensitivity can develop soon after exposure or many (30–40) years later. Of those working around beryllium, about 10% become sensitized, and around half of these progress to develop chronic berylliosis (Fontenot, 2018; Drobyshev et al., 2019).

Mercury-derived compounds are worthy of special consideration; they are still present in the human environment, particularly as dental amalgams (Bengtsson and Hylander, 2017; Bjørklund et al., 2020). Dental amalgams consist of elemental (liquid) mercury mixed with a metal alloy containing silver, tin, copper, and other metals. By weight, dental amalgam contains about 50% mercury. Mercury leakage from dental amalgams is a real concern (Bengtsson and Hylander, 2017; Bjørklund et al., 2019c). On April 29, 2015, the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission (SCENIHR) reported its opinion on the safety of dental amalgam and alternative dental restorative materials (SCENIHR, 2015; Rodriguez-Farre et al., 2016). The SCENIHR concluded that mercury in dental amalgams is a concern. They reported that excreted and circulating mercury in people with dental amalgams is from 5 to 30 times lower than occupational mercury exposure. However, the opinion document assessed that the concentration of mercury in the adult brain depends on: first, the number of amalgam fillings and second, the accumulation in the fetus liver from mothers with dental amalgams. The impact of mercury accumulation in the neonatal brain is of particular concern due to the very long half-life of mercury (more than ten years) (Björkman et al., 2018; El-Badry et al., 2018).

Genetic differences in enzymes metabolizing mercury may affect mercury concentrations in exposed individuals (Barcelos et al., 2013), even though the problem is still of the utmost importance (Andreoli and Sprovieri, 2017; Snoj Tratnik et al., 2017; Leppert et al., 2019). However, contrary or contradictory reports have also been published (Geier et al., 2009; Maserejian et al., 2012; Wright et al., 2012; Watson et al., 2013; Hibbeln et al., 2018). According to the FDA report mentioned above from September 2019, mercury release from dental amalgams depends on the number of placed or removed fillings (Goodrich et al., 2016; Yin et al., 2016). Some studies have suggested possible systemic effects of mercury from dental amalgams, such as neurodegenerative diseases (Hsu et al., 2016) and autoimmune conditions such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (Stejskal, 2013; Stejskal et al., 2013; Alijotas-Reig et al., 2018).

Mercury toxicity can affect the gut microbiome brain axis (GMBA), and therefore neural development (Zhai et al., 2019). This might occur because gut microbiota is an active player in regulating the toxic property of many metallic species, including mercury (Claus et al., 2016; Guo et al., 2018; Li et al., 2019). Therefore, when dealing with mercury pollution and its impact on global human health, two main focuses must be addressed. Firstly, the role of mercury exposure in pregnant women as hazardous for their children's health. Secondly, the role of the gut microbiome in mercury toxicity.

### 1.2. Potential mechanisms for exposure to metals

Metal ores in the Earth's crust are often bound to sulfur groups. When extracted for industrial use, they are purified and lose their original chemical stability. Some transition metals such as iron, cobalt, zinc, selenium, molybdenum, magnesium, chromium, manganese, and copper are essential for life (Zoroddu et al., 2019). Others, such as beryllium, aluminum, titanium, chromium, nickel, copper, palladium, silver, platinum, gold, and mercury, are widely used in industry and various medical implants. Except for chromium and copper, these metals have no established function in humans (Tan et al., 2016). In living organisms, metals exert their effects in different ways. Several of them have an affinity to bind to sulfhydryl (SH) groups, while others have high affinity to –OH, and/or $NH_2$, groups in proteins, enzymes, co-enzymes, and cell membranes (Aaseth et al., 2015). The metal binding to proteins interferes with cellular processes by several mechanisms, such as changed membrane charge, changed permeability, and triggering the antigenicity of autologous structures and autoimmune or autoinflammatory reactions (Rowley and Monestier, 2005; Bjørklund et al., 2018; Drenovska et al., 2019). For instance, nickel-induced hypersensitivity derives from the Ni(II) ions binding to species-specific histidine residues in Toll Like Receptor 4 that trigger the activation of proinflammatory cytokine gene expression and immune responses in human and other primates (Schmidt and Goebeler, 2011; Zoroddu et al., 2014b). Metals in their ionic form are rapidly bound to proteins in the circulating blood, including endothelial and blood cell membranes, particularly the water-soluble component of lipoproteins (Foulkes, 2000; Van Kerkhove et al., 2010). Usually, the affinity is strongest for SH-containing molecules such as methionine, cysteine, and glutathione. The hemoglobin of red blood cells is particularly rich in SH groups, which further explains how various carriers transport ionic metals via blood. Several metals in lipophilic forms, e.g., elemental mercury ($Hg^0$) and methylmercury, readily pass through the blood-brain barrier (Lohren et al., 2015; Bjørklund et al., 2017). The toxic effects of metals are mediated through various reactions, including free radical formation, cell membrane disturbance, or enzyme inhibition (Bjørklund et al., 2019b). Some metals also bind to mitochondria, thereby impairing cellular respiration (Belyaeva et al., 2008). Depending on genetically determined detoxification systems, an individual may tolerate more or less exposure to a toxic metal before showing adverse effects (Menon et al., 2016; Aaseth et al., 2018).

### 1.3. Metal induced autoimmunity

The immunological effects of metals are either non-specific such as immunomodulation or antigen-specific such as delayed-type hypersensitivity (Stejskal, 2015; Stejskal et al., 2015; Kennon et al., 2019; Kitagawa et al., 2019) and autoimmunity (Aten et al., 1991; Bigazzi, 1999; Guzzi et al., 2008; Zhang and Lawrence, 2016). Metals may act as immunosuppressants (cytostatically) such as gold compounds or as immunoadjuvants (non-specific activation of the immune system) such as aluminum compounds. One example of immunomodulation is the ability of some metal compounds to modify cytokine production in vitro and in vivo. The resulting imbalance between $CD4^+$ T helper cells Th1 and Th2 activation can result in immune dysregulation leading to impaired cell-mediated immunity and/or aberrant humoral immunity that may culminate in autoimmune disease (Zhang et al., 2016; Zhu et al., 2016). It has been reported that lead and mercury compounds can enhance IL-4 production by a Th2 clone (and inhibited Th1 proliferation) in vitro and in vivo, which suggests that these metals may induce an autoimmune response by dysregulating the balance between Th1 and Th2, which can increase the production of antibodies to self-antigens (Pollard et al., 2019; Bjørklund et al., 2020). Th1 and Th2 cells are two fundamental T cell subpopulations, differently associated with proinflammatory cytokine profiles (Th1) and anti-inflammatory cytokine profile (Th2) (Berger, 2000).

Another example is the increase of both the intensity and duration of antigen-specific IgE responses by mercury, platinum, and aluminum compounds (Lindblad, 2004; Tsuji et al., 2019). Metals may also induce allergy in genetically susceptible individuals. Most of these are of type IV (delayed-type hypersensitivity, such as contact dermatitis following contact with nickel), but immediate-type reactions are sometimes also observed (Nakagawa et al., 1978; Savignac et al., 2001). Cellular reactions triggered by metals may occur anywhere in the body where metals are deposited. Traditionally, metal allergy has been diagnosed by a patch test (Scalf et al., 2001; Thomas et al., 2009). This method has, however, several drawbacks, and objective interpretation is difficult. Application of the allergen onto skin may aggravate an existing allergy, and, finally, it also harbors the risk of de novo sensitization (Smith Pease et al., 2002). Lymphocyte transformation test (LTT) has high diagnostic efficiency (87%) for the diagnosis of nickel sensitization. LTT has been used in immunology diagnostics for delayed-type hypersensitivity for decades. Memory Lymphocyte Immuno-Stimulation Assay (MELISA®) has been found particularly useful for the diagnosis of metal allergy in vitro (Stejskal et al., 1999). Several mechanisms are proposed for how metals act within the immune system and induce autoimmunity (Griem et al., 1998; McKee and Fontenot, 2016; Monastero et al., 2018). As mentioned, metals bind to thiols and other groups, and thereby modify proteins, they may, via T-cells activate B-cells and allow the altered self-protein to target autoantibodies (Zhang et al., 2017; Abou-Donia et al., 2018). Due to cross-reactions, the triggered T-cells may also react with the native unchanged protein. Metal-binding directly to major histocompatibility complex II (MHC II) without prior processing by antigen-presenting cells or even directly to the T-cell receptor is also suggested as a mechanism (De Wall et al., 2006). In scleroderma, autoantigens possess metal-binding sites, which after binding will generate free radicals. Free radicals will fragment the auto-antigens, thereby exposing cryptic epitopes, which may then trigger autoimmunity. The metal is not a part of the autoimmune epitope.

There is further evidence that metals may cause aberrant MHC II expression on target cells, inhibit T-suppressor cells, cause alterations in the idiotype-anti idiotype network, and induce heat-shock proteins (Zelikoff, 2016; Falcão and Campos, 2017). These and other factors may play a role in metal-induced autoimmunity.

Autoantibodies occur in systemic and organ-specific autoimmune diseases. Since autoantibodies sometimes occur before the onset of disease, they can be used as predictive markers (Yanagita et al., 2015; Koziol et al., 2018; Steck et al., 2018). Some are disease-specific markers and are used to establish a diagnosis, to record progression and predict the outcome of the disease. Both drugs and heavy metals are known to induce autoantibodies. Treatment with D-penicillamine (D-pen) or quinidine, two lupus-inducing drugs in humans, results in the production of autoantibodies against chromatin antigens in genetically susceptible mice. The heavy-chain-variable (VH) chains of several D-pen or quinidine-induced monoclonal antibodies (mAb) are similar to those of anti-nucleolar mAb obtained from mercury-injected mice. The potential of heavy metals to induce autoantibodies has been extensively investigated in animal models (Maqbool et al., 2017). Both mercury and silver-induced anti-nucleolar antibodies (ANoA) may target fibrillarin in genetically susceptible animal models (Hultman et al., 1989, 1995).

### 1.4. Metal and neuroendocrinology

In susceptible mouse and rat strains, mercuric compounds induce a systemic autoimmune disease characterized by a T cell-dependent polyclonal B cell activation, the production of ANoA, and by the formation of renal immune complex glomerulonephritis (Hultman and Eneström, 1988). The nephrotoxic effects of mercury, glomerular, and tubular injury have also been observed in humans (Li et al., 2010; Bridges and Zalups, 2017). Silver, despite being as effective as mercury in the induction of ANoA production in susceptible mice, does not act as an activator of the immune system (Abedi-Valugerdi, 2009). Mercury may bind to the thiols in the cysteine group of fibrillamin, thereby changing its antigenicity and subsequently induce autoantibody production (Stejskal and Stejskal, 1999). In patients with systemic scleroderma, ANoA in about half of the patients reacted with fibrillamin (Liaskos et al., 2017; Sakkas, 2020). After exposure to mercury, certain strains of rats produced high levels of antibodies to laminin. Antibodies to neuronal cytoskeletal proteins, neurofilaments, and myelin basic protein (MBP) are frequently present in the sera of male workers exposed to lead and mercury (Rapisarda et al., 2016; Yoon and Ahn, 2016). The titers correlated with blood and urinary concentrations of those metals. Similar results were obtained in animal studies. In rats exposed to metals, histopathology may show changes in the central nervous system (CNS) and peripheral nervous system (PNS) as well as astrogliosis (Narayanaswamy and Piler, 2010; Yamagata et al., 2017). Autoantibodies can be used to monitor the neurotoxicity of environmental chemicals, and those immune mechanisms may be involved in the progression of neurodegeneration (Gilani et al., 2015; Chen et al., 2016).

### 1.5. Chronic fatigue syndrome and autoimmunity

In several studies, severe fatigue is considered one of the symptoms of autoimmune diseases (Bjørklund et al., 2019a). Other frequently presenting symptoms are classified as neuropsychiatric symptoms. These symptoms are also found in other diseases such as CFS, fibromyalgia, or MCS. CFS patients often have a central down-regulation of the HPA axis resulting in mild hypocortisolism (Vangeel et al., 2015). Magnetic resonance imaging (MRI) demonstrates areas of white matter hyperintensity in CFS patients more frequently than in healthy control subjects. One hypothesis is that these lesions represent sites of inflammation and/or demyelination (Shan et al., 2016). Similar brain abnormalities can also be seen in single-photon emission computed tomography (SPECT) (Shan et al., 2016). Research indicates chronic immune activation in CFS and related diseases. The most prominent findings are an increased number of $CD8^+$ cytotoxic T-cells that show activation markers. Another finding is a decreased function of natural killer (NK) cells (Hao et al., 2010). Affective and neuroendocrine abnormalities in multiple sclerosis patients may be related to inflammatory activity. Metal exposure may be linked to neuroinflammation (Harry and Kraft, 2008), as well as to psoriasis and atopic eczema (Rice et al., 2014).

Research confirms the beneficial effects of the removal of incompatible dental materials in metal-sensitive patients with CFS-like symptoms (Procházková et al., 2004; Kern et al., 2014; Kristoffersen et al., 2016). However, metals are just one of the environmental agents which may induce T-cell mediated delayed-type hypersensitivity and thus trigger the multiple symptoms observed in these disorders. Other low-molecular-weight compounds that may operate similarly are pharmaceuticals or chemicals such as formaldehyde and isothiazolinones (Martin, 2015). The effects of environmental toxins on the dysregulation of the HPA-axis have been studied in animal models and humans (Stejskal and Stejskal, 1999). Metals may disturb the endocrine axis by binding to crucial targets in the HPA-axis (Fig. 1). Metal-induced inflammation may dysregulate the hypothalamic-pituitary-adrenal (HPA) axis and may thus contribute to fatigue and other non-specific symptoms characterizing disorders related to autoimmune diseases. A significant accumulation of mercury in the pituitary gland has been reported (Rice et al., 2014). Mercury deposits were found in neurosecretory neurons in the rodents hypothalamus, after long term exposure to $HgCl_2$ in drinking water (Villegas et al., 1999).

## 2. Concluding remarks

In the light of current knowledge, it seems plausible that metals, as well as other environmental pollutants, are directly or indirectly

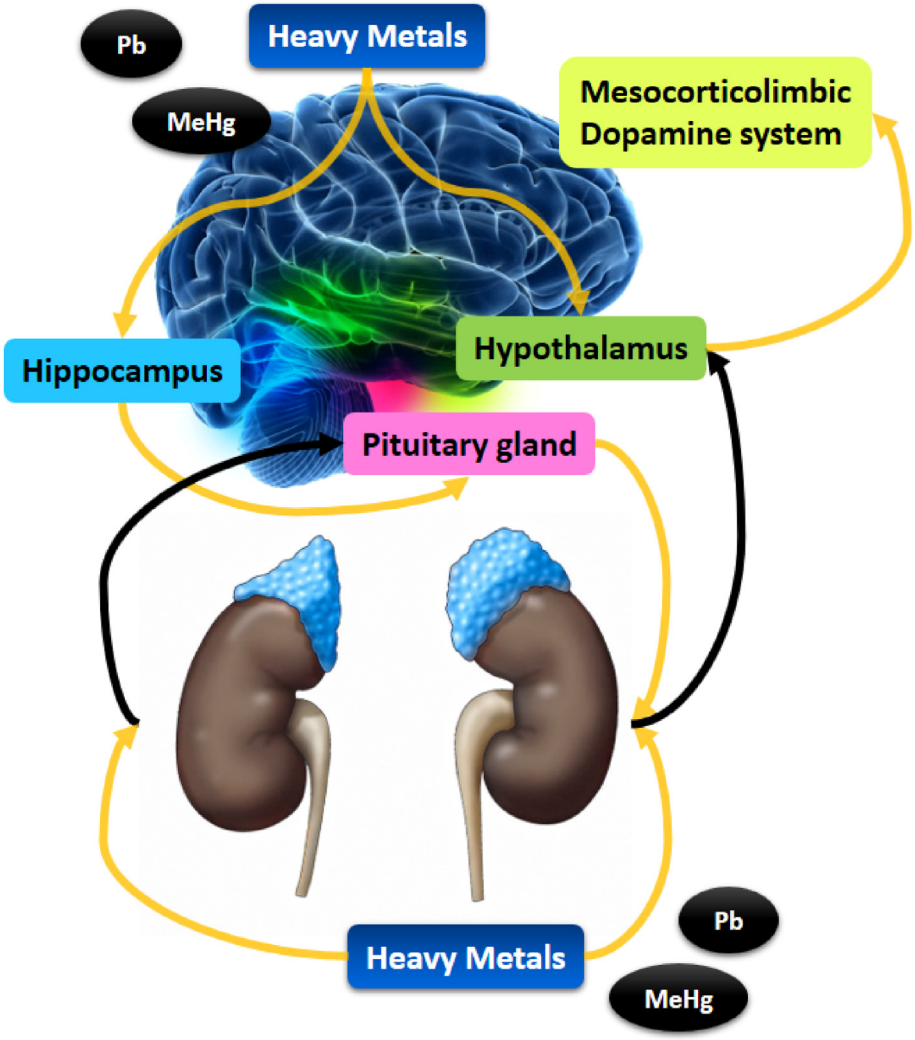


**Fig. 1.** The effects of major neurotoxic heavy metal pollutants. Heavy metals like methylmercury (MeHg) and lead (Pb) can activate the hypothalamic-pituitary-adrenal (HPA) axis, particularly acting on the hippocampal/mesocorticolimbic/dopamine system (neurogenic damage, orange arrows) and via the adrenal/pituitary gland (hypothalamus pathway (black arrows). The two pathways are intertwined and may exacerbate the effects of metals, particularly lead.

involved in the induction or exacerbation of autoimmunity. For example, certain strains of mice develop ANoA anti-bodies to metals, while others do not. In humans, the susceptibility to the effects of xenobiotics may be due to the genetically determined dysfunctions in detoxification systems, including the glutathionylation, acetylation, and other P450-dependent systems, and metallothionein pheno-types. Certain MHC structures may present antigens to helper T-cells more efficiently than others and thus facilitate the development of autoimmunity. Thus, the ability to detoxify xenobiotics, together with the individual susceptibility to the metal, is probably the most critical factor in the outcome of metal exposure. Although animal systems may be important for clarification of several autoimmune mechanisms, they only partially simulate the clinical disease. In humans, both organ-specific and systemic autoimmune diseases persist for years, while in experimental animal systems, autoimmunity is often a transitional phenomenon. To explain this discrepancy, the differences in biochemistry between humans and experimental animals must be considered. Animals used in experimental studies produce their own vitamin C, which might neutralize the pathologic effects of several metals. This may be one factor that makes humans more vulnerable not only to the effects of metals but to other free radical generating substances as well. Possibly, animals not synthesizing vitamin C and thus with biochemistry more similar to the humans in this respect might be more suitable for the study of autoimmunity.

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The authors declare that they have no conflict of interest.

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