

NEUROTOXICITY OF HEAVY METALS IN THE LIGHT OF GENDER STUDIES

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Submitted: 2013-08-15

Accepted: 2014-02-26

Published online: 2014-07-15

Abstract

Gender-related differences regarding susceptibility to chemical exposure to neurotoxicants have not received sufficient attention. Although a significant number of epidemiological studies on the neurodevelopmental effects of metal exposure have been published in the last twenty years, not many of these studies have considered the possible gender-specific effects of such exposure. This review is focused on studies in which the gender differences in pre- and/or postnatal exposures to five metals (mercury, lead, manganese, cadmium, and arsenic) and neurodevelopment were evaluated. A significant number of experimental and epidemiological studies on brain effects of exposure to neurotoxic substances has been published, however not many of them have considered the possible gender-specific effects of such exposure.

Subtle and less subtle differences exist in brain function. They exist due to effects of sex hormones as well as to effects that sex hormones exert on the uterus during development, leading to persisting epigenetic markers. Recent human and animal studies suggest that gender dimorphic profiles are emerging in terms of neurotoxicity, moreover that gender differences in neurotoxicity are more widespread than one may expect. If a risk factor is underestimated in one gender, or if gender specific symptoms are not recognized, timely treatment may be delayed. Knowing that one gender is more vulnerable to poisoning helps to carry out a more effective prevention strategy, that is more efficient than the global approaches. In addition, it has significant consequences on public health concerns and outcomes. Our work is complemented by a critical analysis of some previously published studies.

Key words: *gender – neurotoxicity – heavy metals – children*

INTRODUCTION

In the second half of the 20th century in the social science fields within the feminist paradigm the term gender was introduced to describe the culturally created differences between men and women. The society and its culture affects men and women somewhat differently, leading to socially constructed differences in their behavior, expectations and attitudes. Therefore, the word gender is

a social construct, as opposed to the word sex, which refers to the biological and physiological characteristics that define men and women (Renzetti and Curran 2003).

In the field of social science, gender studies are becoming more prevalent dealing with the analysis of the structures and processes involved in the organization of social relationships between women and men. Gender is a fundamental category of analysis of human organizations and

products of social and cultural life, and gender studies are a dynamically developing field that enriches social science by new insights into the organization of human society.

However, there are also gender studies outside the social science fields (Singer and Denckla 1998, Dluzen and McDermott 2000, El-Khatib et al. 2007). Such work can be seen by the Spanish authors on neurotoxicity of metals in boys and girls (Llop et al. 2013), created under the Seventh Framework Programme of the EU (DENAMIC 2012). It is a meta-analysis of toxicological studies that were available in international databases. The authors provided evidence that there are gender differences in the mechanism of neurotoxicity of heavy metals and they carried out a critical analysis of published literature. Studied heavy metals are also important neuro-toxicants of the environment and they are attributed a great impact on the health of the environment (Patočka and Zölzer 2013). The purpose of this article, the contents of which are primarily the results of a meta-analysis of Llop et al. (2013) supplemented by the results of other studies in this area, is to show the need for such analyzes. The need arises from the fact that gender studies in toxicology provide results important not only from a social perspective, but also from a medical but point of view. The conclusions of such studies not only can assess the risk of exposure to toxic substances in both sexes, but can also influence awareness and education about their risks and significantly interfere with the treatment of poisoning.

MATERIAL AND METHODS

The methods used in this article are the same methods used by the authors of the study Llop et al. (2013). The methodological approach of the author was to trace some current work or neglected information in the MEDLINE databases, Scopus, Scirus and Google Scholar. Llop et al. (2013) used to search for relevant information electronic data sources PubMed (National Library of Medicine, Bethesda, MD, USA: <http://www.ncbi.nlm.nih.gov/pubmed>) and all published clinical studies were searched in which were observed developmental effects of exposure to heavy metals in children under the age of 17. For

an additional search MEDLINE database was used. Search strategies consisted of defining the time interval from January 1, 1991 to December 31, 2012. The following keywords were used for the search: children, metals, lead, manganese, cadmium, arsenic, mercury, neurodevelopment, IQ, sex, gender, or a combination of these keywords.

The criterion for the selection and identification of relevant articles were findings of adverse neurological effects of selected metals published in: a) original articles; b) observational epidemiological studies; c) studies assessing the exposure of one or more selected metals (mercury, lead, arsenic, manganese and cadmium) in the prenatal period or up to 17 years of age; d) longitudinal studies evaluating neurological effects from birth till 17 years of age; e) articles studying neurotoxicity of these metals in both sexes. The study included articles written in English, French, Spanish, Portuguese and Italian. Only the works, of which the statistical significance level was $p < 0.05$ were evaluated.

RESULTS

The criteria set out in the methodology were met by twenty publications. Nine of them were studying mercury exposure, seven exposure to lead, two of them on manganese, two more of them on cadmium and one on arsenic. At the same time there are metals that permanently harm the environment and represent a lifelong burden for the human population.

Mercury in the environment

The input of mercury (Hg) into the environment is contributed mainly by the burning of fossil fuels, the use of mercury in industry and agriculture, and waste handling. A major source of this metal is volcanic activity. The total amount of mercury entering the atmosphere is estimated to be 150,000 tons annually. Approximately two thirds of this amount is attributed to natural sources. In non-contaminated soils mercury concentration falls in the range 0.02–0.2 mg/kg. Mercury passes from soil to plant only in trace amounts. Higher concentrations of mercury are contained in some edible mushrooms, fish and marine mollusks and crustaceans (Mania et al. 2012). The intake

of mercury in the diet is crucially involved in fish consumption where mercury is present in the form of a neurotoxic organic compound – methylmercury (Murata et al. 2011). Just from food only, about 7% of the mercury is absorbed in the small intestine that later accumulates in the liver, kidney and brain. Intoxication by mercury and its inorganic compounds particularly affect the kidney and brain. In the case of methylmercury poisoning neurotoxic effects prevail.

An acute effect of mercury is manifested by disorders of the gastrointestinal tract, diarrhea and salivation, as well as both kidney and central nervous system disorders (Boscolo et al. 2009). Long-term exposure to low doses of Hg results in nervous disorders, loosening and loss of teeth, and kidney disorders. It leads to disorders of sensory functions, speech disorders; there are morphological changes in the brain, mental disorders and an overall change in the psyche. It is suspected that mercury intoxication in the prenatal period could be the cause of autism (Kern et al. 2012). Methylmercury also has teratogenic effects (Holt and Webb 1986). The risk of harm is high and occurs even among mothers, where the concentration of mercury in the hair reaches 15 to 20 mg/kg though poisoning symptoms in adult individuals appear at the concentration of mercury in the hair above 30 mg/kg (Stern 1981). Therefore, in some countries it is recommended for pregnant women to limit the consumption of fish. Sometimes even the exposure to mercury from dental amalgam fillings is considered risky (Rathore et al. 2012), but convincing evidence for this hypothesis is still lacking (Watson et al. 2012).

Exposure to mercury

Nine studies assessed the interaction between mercury exposure and neurodevelopment of boys and girls. Four of them assessed only the prenatal exposure to mercury (Grandjean et al. 1998, Davidson et al. 2004, Gao et al. 2007, Llop et al. 2012), two monitored only postnatal exposure (Cordier et al. 2002, Myers et al. 2009) and three of them the levels of mercury in both periods (Davidson et al. 1998, 2008, 2010). Seven studies that examined neuropsychological effects of prenatal mercury exposure were evaluated in the Seychelles (four cohorts), in China, the Faroe

Islands, and Spain. The exposure assessment was based on the analysis of the mercury concentration in hair samples of mothers (Grandjean et al. 1998, Davidson et al. 2004, 2008, 2010, Gao et al. 2007) and in two studies based on the measurements of the mercury concentration in samples of the cord blood (Gao et al. 2007, Llop et al. 2012). Children ranged in age from a few days after birth (Gao et al. 2007) to 10.7 years (Davidson et al. 2008). Children of the Seychelles cohort were assessed three times: at the age of 66 months, 9 years and 10.7 years (Davidson et al. 2004, 2008, 2010). In three of the seven studies statistically significant gender differences were detected ($p < 0.05$) during prenatal mercury exposure in neuropsychological development. A Chinese study by Gao et al. (2007) points out a negative effect of mercury on the behavior of neonates only in boys. The effect on psychomotor development was found in Spanish children at the age of 14 months (Llop et al. 2012) and effects on learning and memory in the Seychelles children at the age of 66 months (Davidson et al. 2004). These two studies point out that in girls the changes were correlated with the brain development, but no significance was found (Davidson et al. 2004, Llop et al. 2012).

Grandjean and colleagues (1998) observed a statistically significant inverse relationship between prenatal mercury exposure and manual dexterity and attention spans only in boys aged 7 years. Two other studies from the Seychelles, which evaluated the school achievements of children at the age of 9 and visual motor skills at the age of 10.7 years (Davidson et al. 2008, 2010) detected no differences in prenatal mercury exposure among boys and girls.

The neuropsychological effects caused by postnatal exposure to mercury were found in five studies that evaluated the differences between the sexes. Four of them were carried out in a cohort of children born in the Seychelles (Davidson et al. 1998, 2008, 2010, Myers et al. 2009) and one in children born in French Guiana (Cordier et al. 2002). In the Seychelles cohort study neuropsychological examinations were performed in three different time periods (5.5, 9 and 10 years) that were correlated with the content of mercury in the hair. Children from French Guiana were observed in the time period of

9 months to 6 years for neurodevelopmental deviations that were also correlated with the measured concentrations of mercury in their hair.

In studies conducted in the Seychelles cohort were statistically significant gender interactions between postnatal mercury exposure and neuropsychological development of children (Davidson et al. 1998, 2008, 2010, Myers et al. 2009). In boys aged 5.5 years postnatal exposure to mercury was associated with changes in visual-spatial orientation (Davidson et al. 1998) and at the age of 9 years with school performance (understanding of the text and mathematics) (Myers et al. 2009). In girls aged 9 postnatal exposure to mercury was inversely associated with intelligence quotient (IQ) (Myers et al. 2009) and at the age of 10.7 years with visual-spatial orientation (Davidson et al. 2008).

Lead in the environment

Lead (Pb) gets into the environment mainly from burning fossil fuels. Formerly, the most important source in the environment was the traffic. The transition to lead-free fuels leads to its gradual reduction. However, we haven't got rid of lead in the environment from traffic completely. Organic lead compounds pose a greater risk to humans than inorganic lead compounds (Patočka 2008). Agricultural soil has an average of 10 mg Pb/kg. In the leaves of the trees around congested roads still have measured values up to 700 mg/kg. In nature, lead is ubiquitous, including drinking water (Hout 2012). Daily dietary doses of lead found in several studies in European countries range from 27 µg (Sweden) to 180 µg (Belgium). Normal levels of lead in the blood of a human range from 50–120 µg /liter. Tolerable daily dose of lead are 500 µg. While the efficiency of absorption of lead in adults is only about 10%, a child's body absorbs 40–50% of lead through food intake. Lead is therefore especially harmful for children (Patočka and Černý 2003). The level of lead in the blood at 150 µg/liter in children is already a number in which adverse effects appear (slower mental and physical development, reduced learning ability, reduced intelligence, anemia, lowered immunity). In chronic poisoning, the amount of hemoglobin in red blood cells decreases and anemia appears. The absorbed lead is transported through the blood stream to

the liver and kidneys, where it accumulates. During lead poisoning kidneys and liver, blood, nervous and cardiovascular systems can be damaged. Prolonged exposure to lead causes its accumulation in bones, liver, and kidneys. As a result of chronic exposure to lead nervous disorders, indigestion, weight loss, or paralysis of the lower limbs appear (Riva et al. 2012).

Exposure to lead

Seven studies were found dealing with the impact of lead exposure in children aged from 3 months to 7 years in their neuropsychological development (Dietrich et al. 2001, Ris et al. 2004, Jedrychowski et al. 2009). In two of these studies, investigators found a statistically significant relationship ($p < 0.05$) between prenatal concentrations of lead and neuropsychological development of children in both boys and girls. Lead concentrations were inversely associated with the cognitive score – at 36 months of age (Jedrychowski et al. 2009) and the attention and visual-constructive score – at 15–17 years of age (Ris et al. 2004).

Gender-specific relationships between postnatal blood lead concentrations and neuropsychological development were assessed in six studies. Two of them were carried out in the USA (Dietrich et al. 2001, Ris et al. 2004), one in Belgium (Vermeir et al. 2005) and the rest of the Port Pirie cohort was implemented in Australia (Baghurst et al. 1992, Burns et al. 1999, Tong et al. 2000). A statistically significant inverse correlation ($p < 0.05$) was found in a study by Rise et al. (2004). Three other studies discovered a significant negative relationship between different areas of neurodevelopment (behavior, intelligence, abilities, visual-motor performance) and postnatal lead concentrations in boys, although p -value was not statistically significant or not listed (Burns et al. 1999, Tong et al. 2000, Vermeir et al. 2005). An Australian study showed an increased effect of lead in girls (Tong et al. 2000). Baghurst et al. (1992) also discovered that girls at the age of seven years were more sensitive to the effects of postnatal lead exposure than boys. In both genders, an adverse effect of lead was observed, particularly regarding IQ.

Manganese in the environment

Manganese (Mn) is now the second most abundant heavy metal in the earth's crust. It is a hard, brittle metal that occurs in nature in the form of compounds (Palme and O'Neill 2003).

Sources of manganese in the environment are in its ores as well as products resulting from human activity, specifically the waste from the production of manganese, ferromanganese and other metallurgical wastes. Manganese is also used in alloys with other metals. In addition to iron it is also aluminum, copper, magnesium or antimony. In addition to metallurgy and the steel industry, manganese is used in glass or ceramic glazing manufacturing. Manganese is also highly concentrated in certain hydrothermal deposits. There is little information about its secondary use and insufficient attention is given to recycling of this metal. Manganese is used as an indicator of environmental pollution by industry (Wójcik et al. 2004).

Manganese is a biogenic element. In the human body, Mn is present in a concentration of 0.65 mg/kg (Kontur and Fechter 1988). Mn is an element important for blood formation and is involved in the proper development of bones and cartilage. It also helps monitor the cholesterol levels in the blood. Manganese also affects the growth of the human fetus, the development of its organs and the proper functioning of the internal ear, which is important for maintaining balance (Zabłocka-Słowińska and Grajeta 2012). The minimum dose required for a healthy development of the organism is 2–3 mg/day. Information about how much manganese the human body receives in food varies considerably. Most sources state a daily dose of Mn 2–9 mg, but there are values up to about 100 mg/day, especially from drinking water (Bencko and Cikrt 1984). An excess of Mn in the diet has a negative effect on the nervous system and causes symptoms such as Parkinson's disease. Long-term exposure to high doses of manganese can, according to some sources, give rise to Parkinson's disease (Aboud et al. 2012).

Acute toxicity of manganese compounds is generally low and is manifested by effects on the central nervous system, haematopoiesis, kidney and liver (Vieira et al. 2012). After inhalation of MnO_2 or FeMn dust, the

exposed person suffers inflammations of the lungs. Long inhalation of dust containing manganese causes diseases such as silicosis (Hassani et al. 2012). There is an acute danger of poisoning from ingestion of potassium permanganate ($KMnO_4$). $KMnO_4$ causes burns in the digestive tract, kidney inflammation, hepatorenal syndrome and even death. The lethal dose is 5–10 g. Its dust irritates the respiratory system (Young et al. 1996).

Prolonged exposure to elemental manganese and its compounds may cause chronic manganese poisoning, a serious condition called manganisms (Soleo et al. 2012). However, it appears only after months or even years of exposure and is manifested mainly in neuropsychic or neurological disorders: anorexia, drowsiness, restlessness, sexual dysfunction, poor mood, aggression, etc. (Roels et al. 2012). Later convulsive movements appear, rigid facial expressions, incomprehensible speech, tremors, impaired vision, salivation, itching skin, kidney damage, increased thyroid function and other health related issues. Severe manganese poisoning is related to the environment of mines and treatment of manganese ores, and also to the factories for the production of alloys with manganese or to the production of dry zinc galvanic cells (Dressler et al. 2002). The values of Mn in the air are variable 6.10^{-9} mg/ m^3 . Near foundries it may be up to 3.10^{-4} mg/ m^3 . In the work environment its concentration is considerably higher and reaches up to tens of mg/ m^3 (Kondej and Gawęda 2012).

In foods, the content of Mn ranges from tenths to tens, and on rare occasions even to hundreds of mg/kg. The average content in organic of terrestrial plants is given at 30 mg/kg (Abernethy et al. 2010).

Exposure to manganese

There are very few gender studies dealing with the manganese. Two studies conducted in Mexico and Canada evaluated the exposure to manganese in the postnatal period (Riojas-Rodríguez et al. 2010, Bouchard et al. 2011). The amount of manganese was measured in hair and blood samples at the same time with neuropsychological evaluation (children between the ages of 6–13 years). A statistically significant inverse relationship between postnatal exposure to manganese and IQ was found in 7–9 year old girls but not in

boys. Bouchard et al. (2011) found a similar relationship in girls between the ages of 6–13.

Cadmium in the environment

The primary sources of environmental pollution by cadmium (Cd) are iron ore and zinc mining, and also burning fossil fuels and plastics. A major source of this are worn and improperly disposed of lead-acid batteries. It can also penetrate into soil as part of low quality nitrogen and phosphorus fertilizers. Cadmium is characterized by a progressive accumulation in the environment. Accumulation also occurs in sewage sludge, therefore using these sediments as fertilizers may significantly contribute to the contamination of the food chain (Kah et al. 2012). There is also a significant amount of cadmium absorbed by smokers from tobacco smoke (Cooper 2006). The ratio of inhalation exposure to cadmium in smokers is comparable to receiving this element in food (Cd content in tobacco is 1–2 mg/kg). Blood levels of cadmium in non-smokers are 0.2–3 µg/liter, in smokers 0.2–5 µg/liter. Cadmium is toxic for the organism at many levels (Bertin and Averbek 2006). Kidneys, liver and genitals can be damaged. Cadmium is carcinogenic and may cause harm to the fetus (Thompson, Bannigan 2008, Krivosheev et al. 2012).

Its chronic toxicity is significant. Cadmium is one of the most important risk factors for hepatocellular carcinoma (Satarug 2012). The critical organ is the kidney. The digestive tract absorbs only small amounts of cadmium, on average only about 6%, but because its biological half-life is up to 30 years, even small doses of cadmium received over a long period are very dangerous. Cadmium negatively affects calcium metabolism and the production of vitamin D, which can lead to osteoporosis (Youness et al. 2012). As a result of exposure to cadmium we find necrosis and gonadal tumors, renal dysfunction, and disorders of the cardiovascular system.

Exposure to cadmium

There was only one study found on the gender relationship between exposure to cadmium and neuropsychological development of the child. In this study the prenatal maternal exposure to cadmium in relationship to neuropsychological development of the child

was assessed (Kippler et al. 2012a, b). A statistically significant inverse relationship was found between the amount of cadmium taken by mothers during pregnancy and their daughters' IQ at the age of 5 years.

Arsenic in the environment

Arsenic (As) is present in the environment in organic and inorganic forms, and in particular in the form of sulfides and it is found in various rocks and soils. The inorganic arsenic gets into water by leaking from rocks, from wastewater and atmospheric deposition. It is a normal part of ground and surface water. The concentration in water ranges from 1–2 µg/liter; in the areas where there are natural resources, it may be considerably higher, up to 12 mg/liter. Daily intake in drinking water in the Czech Republic is below 10 µg everywhere, but there are countries such as Bangladesh, where often the only source of water (artesian wells) contains excessive amounts of arsenic. Contamination of groundwater by arsenic is also a problem in India, China, Argentina, Chile, Mexico, Thailand and USA, but not to the extent as in Bangladesh, where it is the highest in the world. Millions of people there do not have other sources of drinking water and arsenic-contaminated drinking water is used by 25 million people in Bangladesh (Cilek 1998).

Acute arsenic poisoning in high doses may occur as a paralytic form with severe headaches and circulatory collapse. In these cases, death can occur within hours. At lower doses common symptoms appear like headaches, dizziness, weakness, dry mouth, burning pain in the throat after a few hours of vomiting, severe abdominal pain, watery or bloody diarrhoea. It soon may lead to dehydration, low blood pressure, circulatory collapse, the cyanosis and the victim may suffer convulsions and eventually coma and subsequently die (Chen et al. 2011). If the person survives the acute phase, usually on the second or third day jaundice and anuria set in. There is then serious liver and kidney damage. Chronic poisoning is characterized by a diverse series of clinical symptoms. These are symptoms of irritation and inflammation of the skin leading to the formation of deep ulcers. Thickened skin appears on the palms and soles. Frequently there is hair loss and damage or loss of nails. For chronic arsenic

poisoning dark bronze skin coloration (melanosis) is characteristic. Frequently there is also swelling of the eyelids (Rahman et al. 2009).

Exposure to arsenic

We have found two studies regarding arsenic exposure on neuropsychological indicators evaluating the differences between genders. One of them was carried out in Bangladesh (Hamadani et al. 2011) and the other in Mexico (Rosado et al. 2007). Hamadani et al. (2011) assessed exposure to arsenic in the 8th and 30th week of pregnancy and correlated it with the neuropsychological development of children up to 5 years of age. In girls arsenic decreased the IQ.

Rosado et al. (2007) continuously measured the concentration of arsenic in the urine of children between the ages of 6–8 years and they correlated the values with a range of neurodevelopmental indicators. A statistically significant inverse correlation was found between postnatal exposure to arsenic and the score in solving tests: in boys in verbal test and attention spans and in girls a memory test was used. Statistical significance was not published, however.

DISCUSSION

In this paper we discuss the five most common sources of heavy metals (mercury, lead, cadmium, manganese and arsenic) in the environment and the clinical symptoms of acute and chronic intoxication in humans. Based on a literature survey, this paper graded gender differences in pre- and postnatal exposure to these metals and their impact on neurodevelopmental parameters of newborns. The discussion is based on the works summarized in the meta-analysis of Spanish authors Llop et al. (2013) and also on other information researched by the author of this article.

The largest amount of literature on possible neurodevelopmental effects on children exists on exposure to mercury, but clear reasons for the differences in Hg neurotoxicity related to both genders is not clear. The significance of the evidence does not support a clear view of gender differences in the effects on the nervous system. In some studies boys seem to

be more affected (Grandjean et al. 1998, Gao et al. 2007, Davidson et al. 2010), in others girls (Davidson et al. 1998, 2008).

There are similar results of experimental studies on laboratory animals exposed to mercury. In some studies regarding prenatal exposure to mercury, changes in learning and behavior have been found in rodents (Onishchenko et al. 2007) and changes in physical activity in human males (Giménez-Llort et al. 2001, Yoshida et al. 2005). In contrast, other studies have found disorders in physical activity, working memory (Goulet et al. 2003) and the ability to learn (Yoshida et al. 2005) in females. A clear case of gender differences in the effects of mercury has not been elucidated not even in other studies (Cauli et al. 2013). In studies on postnatal mercury exposure in males, there was detected an increased frequency of antisocial interactions, but in females, on the contrary, the frequency of antisocial interactions decreased (Olczak et al. 2011).

There is also plenty of information available about the specific effects of lead on both genders. The works examined in this study show that in many studies (Burns et al. 1999; Ris et al. 2004, Vermeir et al. 2005, Jedrychowski et al. 2009), neurotoxic effects of lead appear to be more pronounced in boys than girls, but not in all cases (Baghurst et al. 1992, Tong et al. 2000). Most experimental studies on animals have also shown that lead has a greater influence on neurodevelopmental parameters in males than in females (Yang et al. 2003, de Souza Lisboa et al. 2005, Soeiro et al. 2007, Mansouri et al. 2012).

Information regarding gender differences in susceptibility of boys and girls to manganese, cadmium and arsenic are still very limited. However, completed studies indicate that girls may be more sensitive to the action of these three metals than boys. Two studies evaluated the differences between the genders regarding postnatal neurotoxicity of manganese (Riojas-Rodriguez et al. 2010, Bouchard et al. 2011) and in both studies, a significant negative impact on girls was observed. Increased sensitivity to exposure to manganese in males, on the contrary, was observed in several animal studies (Simon et al. 1994, Moreno et al. 2009, Madison et al. 2011). Differences in susceptibility of animals to manganese may be associated with a

reduction in the striatal dopamine response (Simon et al. 1994, Moreno et al. 2009) in males or different morphology of neurons in the striatum of males and females (Madison et al. 2011).

The only published work on the neurotoxic effects of cadmium in the early postnatal period shows stronger negative effect on the IQ of girls (Kippler et al. 2012a). The authors provided this finding in relationship to the other observation that mothers of girls with higher cadmium levels in the body have lower birth weight and smaller head circumferences (Kippler et al. 2012b). Studies on animals did not show any gender differences.

Concerning the impact of pre- and postnatal exposure to arsenic on children's neurodevelopment, there are only two such studies. One involves a negative association with IQ in women (Hamadani et al. 2010), and the second study (Rosado et al. 2007) finds that some indicators of neuronal development are more negatively involved with boys (problem solving, vocabulary and attention), rather than in girls (memory). Experimental studies show that spontaneous locomotor activity in female rats was affected by chronic exposure to low doses of arsenic over the activity of males (Bardullas et al. 2009).

The explanation of gender differences in exposure to heavy metals is not easy. Experimental and epidemiological studies are still rare, not always providing clear unambiguous results and this can only lead to speculation. However, there are at least three possible mechanisms by which these metals can cause differences in neurotoxicity between the two genders.

The first one is related to the metabolism of these metals, particularly their intake and excretion. It was observed that female rodents accumulate more mercury in the brain and males accumulate more in the kidneys. But it is not clear whether this is due to differences in the accumulation or elimination from different tissues (Ekstrand et al. 2010). Higher average tissue concentrations of cadmium in women compared with men are primarily the result of a generally higher intake of cadmium from the digestive tract of women (Vahter et al. 2007). In women higher methylation of inorganic arsenic was also observed (Vahter et al. 2002).

Another explanation for the gender differences in neurotoxicity of heavy metals lies in the possible interaction with hormones and neurotransmitters that are different in the two genders. Abdelouahab et al. (2008) found gender differences in the effects of mercury and lead on the level of TSH (thyroid stimulating hormone). A negative influence of both metals to TSH was observed only in females. Conversely, a positive effect was only observed in males. It is commonly known that some brain areas in men and women may develop in different ways, which could be the reason for gender differences in the neurotoxic effects of chemical substances (Scallet and Meredith 2002). For example, perinatal exposure to thiomersal (mercury compound used for the preservation of vaccines) causes hypothyroidism and decreases motor learning skills only in male rats (Khan et al. 2012, Sulkowski et al. 2012). Prenatal exposure to low doses of lead disturbs the dopamine system (Leasure et al. 2008) and increases the myoinositol signal of the hippocampus (Mansouri et al. 2012) only in male mice.

The third mechanism is related to the ability of heavy metals to cause oxidative stress in the developing brain. Reactive forms of oxygen may regulate the inhibition of the Na^+/K^+ -ATPase activity in the neuronal membrane, which plays a critical role in maintaining cellular ionic homeostasis and physiological functions of the nervous system (Yin et al. 2007). Huang et al. (2008) found gender differences in the effects of mercury on the auditory response in mice. Males were more sensitive to mercury and the changes of auditory responses correlated with increased lipid peroxidation and changes of Na^+/K^+ -ATPase activity in plasma and brain stem of the animals. Gender differences were also found in several other enzymes such as NADPH oxidase (Miller et al. 2007) or alcohol dehydrogenase (Kimura et al. 2011).

CONCLUSION

Gender studies in disciplines outside the realm of social sciences, are not very common. But the studies that were not primarily directed at gender and had a different design, can derive some important differences between

the genders and interpret them as gender, not sexual. Such an attempt has been made to the toxicological effects of several heavy metals that are a normal part of our environment and which, according to current knowledge, significantly interfere with our environmental health. Because heavy metals are hazardous environmental pollutants in many countries around the world, it would be helpful in this direction to focus on the education of children

and adults, and to plan epidemiological, environmental and toxicological studies so that they are able to reflect gender differences.

ACKNOWLEDGEMENTS

The article was created within the project EPZ2012_003 ZSF JU in České Budějovice.

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