Azerbaijan Journal of Physiology, vol. 37, No 1, pp. 7-16 (2022)

İCMALLAR | REVIEWS

https://doi.org/10.59883/ajp.5 UDC 612.821.4+615.21

THE EFFECTS OF HEAVY METALS ON THE DEVELOPING BRAIN

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The present paper reviews the works on the combined effects of heavy metals (HMs) with other HMs, stress, and neurotropic drugs on the developing central nervous systems of humans and animals performed over the past 30 years. The analysis shows that there are disproportionately few works on the mentioned joint effects of HMs in relation to the importance of this issue. It was found that the joint administration of HMs with each other and under stress increases the neurotoxic effect of metals on the brain of animals. A greater vulnerability to the neurotoxic effects of HM mixtures on the developing brain was also noted. Neurotropic drugs in combination with HMs have multidirectional effects. Thus, along with the counteraction of the reference nootropic piracetam to the inhibition of the avoidance response in rats, which is exerted by HMs, there was an increase in the neurotoxic effects of lead and cadmium salts when combined with that nootropic. Combined administration of Semax (a regulatory peptide with nootropic effects) and molybdenum, which separately suppressed the avoidance response in rats, paradoxically improved learning and memory. The revealed unpredictability and enhancement of the neurotoxic effects of HMs when combined with neurotropic agents are fraught with danger to human health in regions with developed industries. This is especially important for the health of children due to the increased vulnerability of their developing brains to neurotoxicants.

Key words: heavy metals, developing brain, stress, neurotropic agents, learning, memory

The intensive development of industry is accompanied by the accumulation of a huge amount of waste in the environment, which poses a significant threat to humans and animals. This is especially true for regions with a large number of industrial enterprises on their territories. The most common and dangerous pollutants are the all-pervading supertoxicants - heavy metals (HMs), which have long had adverse effects on the body [1, 4, 5].

It should be noted that in areas without excessive industrial development, such as, for example, Lebanon, the issue of HMs is also beginning to attract attention. These toxicants are found in food additives, breast milk, coffee, alcohol, cigarette smoke, and other sources [12, 34, 39, 61, 63].

The main anthropogenic sources of pollution are enterprises of ferrous and non-ferrous metallurgy, thermal power plants, motor vehicles, and the petrochemical industry. Water contamination with HMs occurs through the disposal of wastewater from galvanizing plants, mining, ferrous and non-ferrous metallurgy, as well as machine-building plants. Man-made disasters pose a great danger to mankind, the destructive consequences of which have recently been commensurate with wars.

Technogenic emissions of HMs into the biosphere are constantly increasing. In ancient times, only 18 chemical elements were used by people, by the 17^{th} century they become 25 of them, and by the 20^{th} there were already 80. During the first half of the last century, much more minerals were extracted from the bowels than in the entire history of mankind. As a result, the concentration of HMs in industrially developed regions exceeds the background levels ten times, while near large sources of emissions it can surpass hundreds and thousands of times [7]. According to V.I. Vernadsky, over time, the scale of human activity became comparable to the geological forces that transform nature. This led to the disturbance of the dynamic equilibrium of ecosystems as well as the introduction into the environment of uncharacteristic physical, chemical, and biological agents that have a toxic effect on the biota of the environment, which causes a decrease in biodiversity and creates problems with obtaining ecologically safe food [3]. This state of affairs threatens with unpredictable consequences since the existing capacity of nature for self-cleaning is exceeded.

For HMs, in principle, there are no self-cleaning mechanisms. They only move from one natural reservoir to another, interacting with various living organisms. They pose the greatest danger to humans since the latter are at the top of the food chain, and, as a result, they receive products whose concentration of toxicants is 100–10,000 times higher than in soils [6]. In particular, HMs have a particularly strong effect on the central nervous system (CNS). This is due to the fact that they cause lipid peroxidation, which occurs most intensively in the CNS. It can be elucidated by the high content of polyunsaturated fatty acids in the brain, which serve as a substrate for lipid peroxidation, and the high concentrations of metal ions with variable valence, which enhance this process.

HMs affect the body not in isolation, but in combination with other factors, such as other HMs, stress, drugs, etc. In view of this, the need to analyze their joint effects has been increasingly emphasized recently [14, 21, 23, 36]. Recent work on the combined effects of chemical agents has opened an "exciting era" in the evolution of toxicology [49]. Such kind of works is necessary not only for understanding the possible health hazards of the combined effects of HMs, but also for a successful analysis of the mechanisms of their action.

The aim of the study is to analyze the works on the cumulative effects of heavy metals, along with other HMs, stress, and neurotropic drugs, on the developing brain of humans and animals performed over the past 30 years.

Human exposure to mixtures of various HMs is widespread, especially near mining waste [56]. Thus, drinking water and air contain a mixture of a large number of chemical components, including HMs. Nevertheless, for a long time, the interaction of the latter was not a subject of study [2]. One of the reasons for this is the difficulty of studying such an effect of HMs on the body and the lack of adequate models [18]. However, despite this, the study of the joint effects of HMs prevailed over time.

Initially, the works described the analysis of possible research strategies, new models, and methods of analysis. In addition, the combined effects of chemical agents were considered with respect only to substances present in water, air, cigarette smoke, etc. [26, 27, 45, 57]. Obviously, this made it fundamentally impossible to evaluate the results of the joint effects of specific HMs on the human body.

Air attracts the attention of researchers due to the fact that it is the only one of all sources through which pollution enters the body continuously. According to the WHO, it causes over 3 million premature deaths annually [47]. Among the targets of exposure to polluted air is the CNS. In particular, it has been shown that air pollution can cause Alzheimer's and Parkinson's diseases [16, 17, 29, 43, 50, 51].

It should be noted that in addition to various metals, air contains dust particles, organic compounds, etc. This makes it impossible to assess the contribution of various specific HMs separately and the role of their combined effects on human health. This can only be done in experiments on animals, which makes it possible to control the HM mixtures used, in particular to evaluate the effects of HMs separately as well as their combinations. It should be noted that despite the increase in this kind of studies, there are still disproportionately few of them compared to the importance of the issue, even when it is emphasized in the corresponding works [9].

Recently, much attention has been paid to the study of the impact that the environment has on children [14, 25, 40, 44, 58]. This is due to the particular vulnerability of the immature, developing CNS. That was first noted in 1975, when the hypothesis was formulated that the nervous tissue during its development is more vulnerable to chemical attack than at any other time [60]. Subsequently, a lot of data were obtained indicating a greater vulnerability of children's CNS to the effects of HMs [13, 41]. The latter is due to several reasons. First, intrauterine development is already exposed to HMs. Thus, it has been established that there is a strong correlation between the maternal blood lead level and the umbilical cord blood lead level, indicating the transmission of HMs from the mother to the fetus [28, 44]. It has been shown that arsenic, lead, and cadmium penetrate the immature blood-brain barrier and accumulate in the developing brain [67]. The greater vulnerability of children to toxic effects can also be elucidated by the fact that their brains grow and develop, which is associated with the processes of proliferation, differentiation, migration, myelination, synaptogenesis, and apoptosis of nerve cells [55].

Further, children spend a lot of time playing on the ground, in the sand, inhaling flower pollen, etc. A child's body absorbs up to 40% of lead from food and water, while an adult's body absorbs only up to 10%. In addition, in adults, lead is deposited mainly in the bones, while in children, up to 30–40%, it accumulates in the internal organs and in the brain tissue. Up to 90% of lead is excreted from the body of adults, but only up to 60% in children [1]. It is emphasized that children, per unit of body weight, eat and drink more than adults [40].

In virtue of the above, the body of the newborn is already weakened; many diseases of the CNS are formed in childhood, including those that result from exposure to HMs. In particular, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases arise from exposure to HMs in childhood [48, 53]. That has been supported by evidence from experiments on animals. Thus, the results of experiments on monkeys made it possible to conclude that the pathogenesis of Alzheimer's disease in old monkeys is due to exposure to lead in their childhood [66]. The obtained results also allowed the authors to point out the existence of a kind of "epigenetic imprinting" that occurs at an early age and affects the expression of genes, which further correlates with Alzheimer's disease. Subsequently, the idea of the existence of periods critical for such a neurotoxic effect was developed [24, 33].

With regard to the importance of the above-described issue, a set of studies related to the neurotoxicity of a developing organism has received recognition as a new direction in toxicology: "Developmental Neurotoxicology". To date, a large number of reviews related to this area have been published [19, 30, 31, 37, 65]. Generalizing works have been published that indicate that the combined effects of HMs are critical for the health of children [20, 56]. However, there are few studies on the combined effects of HMs, especially in comparison with the effects of each of the HMs included in the mixture, in this area as well.

In 455 Mexican children, the effects of combined exposure to lead and manganese were analyzed in early childhood, during the period of rapid brain development and its increased sensitivity to neurotoxicants. At the ages of 12 and 24 months, the blood levels of the selected HMs were measured and compared with the development of the brain at an interval of 6 months. Research has shown that the interaction of lead and manganese in early childhood causes greater neurotoxic effects than each metal alone [21]. The authors consider a change in calcium metabolism, their common target, as a mechanism for such a synergistic action of those agents. Taking into account that they are often found together in the environment [8], the authors of the study propose to consider their joint action as a threat to health.

The authors also noted that at the age of 12 months, the effects of metals were greater than at 24, which was regarded as evidence of the existence of a critical period for such exposure. It was also found that the neurotoxic effect of lead is more pronounced in children with an increased blood level of manganese. A mixture of these HMs was also investigated in another work. A comparison of the concentrations of lead and manganese, on the one hand, and the IQ of 261 children from Korea aged 8–11 years, on the other, led to the conclusion that there is an additive interaction between these metals that affects the mental abilities of children [38].

Despite the importance of the issue, there are also few works on the study of the effects of HM mixtures on the offspring of animals. It was found that the combined effects of lead and cadmium on female rats caused changes in the dopamine and serotonin systems of the hippocampi of the offspring that persisted for a long period, as well as an increased anxiety level in the elevated plus maze [42]. It has also been shown that perinatal exposure to these metals causes additive inhibition of several enzymes essential for the normal functioning of the CNS and affects neurochemical changes in the striatum and cerebellum, which are associated with changes in motor activity in adult rats [10, 11]. The synergism of these heavy metals is also manifested during their absorption in the cells of the cerebellum, cortex, and hippocampus, leading to an increase in the neurotoxic disturbance of the developing CNS of rats under the effect of certain metals [32]. Later, a direct synergistic inhibition of learning and memory in rats by arsenic, cadmium, and lead was found [52].

This synergy is not always observed. So, in the work published in 2012, it was found that when pregnant rats were exposed to lead and manganese together, a multidirectional effect was observed in their offspring. In females, learning in the Morris test was worse than in the case of separate administration of these metals, while in males it was better. The authors explain the latter by the work of the compensatory mechanism, which is triggered in the case of a greater toxic load [15].

Using an electron microscope, it was found that the combined effects of lead and cadmium on female rats during pregnancy and lactation led to a greater (when compared to separately used metals) impairment of the ultrastructural organization of the brain in offspring (swelling of mitochondria, destruction of organelles, etc.), a decrease in the activity of antioxidant enzymes (superoxide dismutase, catalase, etc.), and an increase in the activity of malondialdehyde as an oxidative stress marker [68]. There are also studies on the effects of small doses of lead, mercury, cadmium, and arsenic, administered separately and in combinations, on mice at the age of 3 weeks. It was found that a mixture of the first three metals reduced brain weight and caused neuronal degeneration [22].

HMs can act together not only with each other but also with other factors, such as stress, in particular maternal stress, which can also affect their neurotoxic effects. Thus, exposure of stressed females to lead negatively affected their brain's mesolimbic dopamine / glutamate systems involved in cognitive functions [62]. Later, up to the present day, many examples were given of the negative joint effects of those factors on the development of offspring [54, 59]. However, we did not find any work on the joint effects of HMs and neurotropic agents on the developing brain.

Another factor is neurotropic drugs, which are widely used by both adults and children. This issue has not received due attention, although the effects of such combined use are unpredictable. Thus, the combined use of the nootropic piracetam with lead and cadmium salts, along with an improvement in the development of the avoidance response, caused an aggravation of the inhibition of learning and memory in rats [36]. An unpredictable result was obtained when studying the combined effects of Semax (a fragment of ACTH with nootropic properties) with molybdenum on the formation of avoidance response in rats in the shuttle-box. It was found that both the drug and HMs slowed down the development of the response. At the same time, their combined use paradoxically improved learning and memory [35]. Such unpredictability is fraught with danger to human health, especially in regions with developed industries.

Thus, the analysis shows that there are disproportionately few works on the combined effects of HMs with each other and with such factors as stress and neurotropic drugs in relation to the importance of the issue. The data obtained in those works indicate a change in neurotoxic effects when those factors act together, including their enhancement, which poses a danger to human health. This is especially important for the health of children due to the high vulnerability of their developing brains to neurotoxicants.

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AĞIR METALLARIN İNKİŞAF EDƏN BEYİNƏ TƏSİRİ

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İnsan və heyvanların inkişaf edən mərkəzi sinir sisteminə ağır metalların (AM) digər AM-larla, stress və neyrotrop preparatlarla birgə təsiri haqqında son 30 il ərzində aparılmış işlər təhlil edilmişdir. Aparılan təhlil onu göstərir ki, AM-ların sözügedən birgə təsiri haqqındakı işlərin sayı, bu məsələnin vacibliyi ilə müqayisədə qeyri-mütənasib şəkildə azdır. Müəyyən edilmişdir ki AM-ların bir-biri ilə və stresslə birgə tətbiqi metalların heyvanların beyninə neyrotoksik təsirini artırır. İnkişaf edən beynin AM qarışıqlarının neyrotoksik təsirinə daha yüksək həssaslığı qeyd edilmişdir. Neyrotrop preparatların AM-larla birləşmələri müxtəlif istiqamətli təsir göstərirdi. Belə ki, siçovullarda AM-ların göstərdiyi uzaqlaşma reaksiyasının yavaşlamasına pirasetamın etalon nootropunun əkstəsiri ilə yanaşı, bu nootropun kadmium və qurğuşun duzları ilə birləşmələrinin neyrotoksik təsirinin güclənməsi aşkar edilmişdir. Baxmayaraq ki, semaxın (nootrop təsirləri olan tənzimləyici peptid) və molibdenin birgə tətbiqi siçovullarda uzaqlaşma reaksiyanın yaranmasını ayrı-ayrılıqda qarşısını alıb, təlim və yaddaşı paradoksal şəkildə yaxşılaşdırdı. Müəyyən edilmiş gözlənilməzlik və AM-ların neyrotrop agentlərlə birləşməsindən yaranan neyrotoksik təsirin güclənməsi sənayenin inkişaf etdiyi regionlarda insanların sağlamlığına təhlükə yaradır. İnkişaf edən beynin daha yüksək həssaslığı ilə bağlı olaraq, bu məsələ uşaqların sağlamlığı üçün daha vacibdir.

Açar sözlər: ağır metallar, inkişaf edən beyin, stres, neyrotrop preparatlar, təlim, yaddaş.

ВЛИЯНИЕ ТЯЖЕЛЫХ МЕТАЛЛОВ НА РАЗВИВАЮЩИЙСЯ МОЗГ

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Анализированы работы о совместном воздействии тяжелых металлов (ТМ) с другими ТМ, стрессом и нейротропными препаратами на развивающуюся центральную нервную систему человека и животных, выполненные за последние 30 лет. Анализ показывает, что работ об указанном совместном воздействии ТМ остаётся непропорционально мало относительно важности данной проблемы. Установлено, что совместное введение ТМ друг с другом и со стрессом усиливало нейротоксическое воздействие металлов на мозг животных. Была отмечена также бóльшая уязвимость к нейротоксическому воздействию смесей ТМ на развивающийся мозг. Нейротропные препараты в сочетании с ТМ оказывали разнонаправленное действие. Так, наряду с противодействием эталонного ноотропа пирацетама ингибированию реакции избегания у крыс, которое оказывают ТМ, было отмечено усиление нейротоксического действия солей свинца и кадмия при их сочетании с этим ноотропом. Комбинированное введение семакса (регуляторного пептида с ноотропными эффектами) и молибдена, которые по отдельности подавляли выработку реакции избегания у крыс, парадоксальным образом улучшало обучение и память. Обнаруженные непредсказуемость и усиление нейротоксического действия ТМ при их сочетании с нейротропными агентами чревато опасностью для здоровья человека в регионах с развитой промышленностью. Это особенно важно для здоровья детей в связи с повышенной уязвимостью их развивающегося мозга к нейротоксикантам.

Ключевые слова: тяжелые металлы, развивающийся мозг, стресс, нейротропные препараты, обучение, память.

Çapa təqdim etmişdir: Aliyə Azat Qaysina, t.ü.f.d., dosent.
Redaksiyaya daxil olma tarixi: 03.02.2022.
Təkrar işlənməyə göndərilmə tarixi: 12.02.2022.
Çapa qəbul edilmə tarixi: 18.04.2022.