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ACUTE EFFECTS OF LEAD, MERCURY AND MANGANESE ON THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM IN RATS IN COMBINATION WITH ALCOHOL EXPOSURE*

András PAPP, László PECZE, and Tünde VEZÉR

University of Szeged, Department of Public Health, Szeged, Hungary

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Heavy metals, due to their numerous applications in industrial processes, agrochemicals and household articles, have caused a widespread pollution and can be found in different foods. One of their target organs is the central nervous system. The toxic effects of heavy metals can be modified by lifestyle-originated factors such as consumption of alcohol. The aim of this study was to investigate the changes in spontaneous cortical activity (ECoG), cortical sensory evoked potentials (EPs) and peripheral nerve action potentials, recorded in rats pre-treated with alcohol and acutely treated with lead, mercury and manganese by intraperitoneal injection. In the ECoG, Hg²⁺ caused a massive shift to lower frequencies while the effect of Mn²⁺ and Pb²⁺ was slight, and alcohol pre-treatment altered the effect of the metals minimally. The amplitude of EPs increased upon the application of heavy metals, and the peak latency lengthened. The effect of Hg²⁺ was the strongest and that of Pb²⁺ the weakest, and these effects were potentiated by alcohol. Exposure to heavy metals, together with alcohol consumption, can aggravate the known neurotoxic effects.

KEY WORDS: *cortical activity, heavy metals, neurotoxicity, peripheral activity*

Heavy metals, due to their numerous application in industrial processes, agrochemicals and household articles, have caused a widespread pollution and can be found in food and drinking water.

Lead, after long years of use in paint and car fuel, resulted in widespread environmental contamination and accumulation of the metal and in repeated episodes of lead poisoning (1). The adverse effect of chronic Pb exposure on mental development of children (impaired IQ, behavioural difficulties) is well known. *Otto et al.* (2) found characteristic EEG and auditory evoked potential alterations in children with lead burden. In our earlier work, subchronic Pb²⁺ treatment of rats resulted in altered spontaneous and evoked cortical activity (3, 4).

The neurotoxicity of mercury has been observed at different levels of the nervous system. Workers with occupational exposure to Hg²⁺ showed alterations to the cortical electrical activity (slow-wave EEG; 5), amplitude increase in the somatosensory evoked potential (6) or delayed waves in the brainstem auditory evoked potential (7).

In animal experiments, elevated levels of transmitter noradrenaline (8), dopamine and serotonin (9) were observed in rats treated with Hg²⁺. Ligand binding of muscarinic receptors was inhibited by Hg compounds in rat cortical neuronal membranes *in vitro* (10). In our earlier studies, rats receiving daily Hg²⁺ doses of 0.4 mg kg⁻¹ and 1.6 mg kg⁻¹ for 4 to 12 weeks showed

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alterations in the spontaneous (11) and stimulus-evoked (12, 13) cortical activity.

Manganese in micro amounts is essential for living organisms, but is toxic when overdosed (14). High Mn levels (ore dust, metal fumes) are an occupational risk factor. The presence of Mn in the general environment is slowly increasing due to human activity such as the use of the organo-metal manganese compound MMT as anti-knock petrol additive in certain countries (15), agricultural application of Mn-containing fungicides (16), and spent dry cells in the communal waste. In manganism, a chronic disease resulting from long-term high-dose occupational exposure to manganese, a Parkinson-like syndrome with motor abnormalities (slowed motion, increased muscle tone) develops (17), with functional (18) damage to the dopaminergic systems. However, there have been but a few reports on neurological (EEG and/or evoked potential) disturbances following occupational (19, 20) or accidental (21) Mn exposure.

Recently, there is a growing awareness that the absorption and accumulation of heavy metals, and the susceptibility of animals and humans to their toxicity, is influenced by a number of nutritional, physiological and environmental factors (22). One such factor is ethanol, the effect of which on the toxicity of the heavy metals has not yet been established clearly. In case of a number of other toxicants, alcohol has been reported to enhance carcinogenicity, mutagenicity and hepatotoxicity (23). Heavy use of alcohol in humans is associated with elevated blood Pb concentration (24, 25), possibly because ethanol enhances its absorption (26). Ethanol potentiated the toxicity of methylmercury in rats, manifested in neurological signs (hind leg crossing and abnormal gait) and mortality (27). Mn is engaged both in generating reactive oxygen species and in protecting against oxidative damage – e.g. oxidative stress induced by ethanol (28) – by breaking down superoxide anions (29).

This study investigated the changes in the spontaneous activity (electrocorticogram, ECoG) and stimulus evoked potential (EP) of the somatosensory cortex and in the compound action potential of the tail nerve in rats subchronically pretreated with alcohol and acutely treated with the heavy metals lead, mercury or manganese.

METHODS

The experiments were performed on adult male Wistar rats (ca. 350 g b. w.) in groups of eight

animals each. The animals were kept under standard conditions with food and water *ad libitum*. Alcohol-pretreated animals had 5 % (v/v) ethanol in their drinking water for 3 to 4 weeks before being used. In a previous study (3) it was found that ethanol alone had no significant effect on the neurophysiological parameters to be investigated.

Preparation and recording was done under urethane (1000 mg kg⁻¹ b. w. ip.) anaesthesia. The head of the rat was clamped in a stereotaxic frame and the left hemisphere was exposed. After a one-hour recovery from surgical intervention, a silver recording electrode was placed on the somatosensory projection area of the whiskers. The contralateral whisker pad was stimulated using square wave electric pulses (ca. 4 V, 0.05 ms, 1 Hz). Recording and evaluation of the electrical activity was PC-based using the NEUROSYS software (Experimetria Ltd., UK). The cortical activity records consisted of a five-minute electrocorticogram (ECoG) taken from the barrel field, followed by evoked potentials (EPs) obtained by a train of 20 stimuli delivered to the whiskery skin. The EPs were averaged, and the latency and amplitude measured. From the ECoGs, band activity (standard, delta to gamma) (30) was automatically determined and the so-called ECoG index [ratio of the low and high frequencies in the ECoG: (delta+theta)/(beta1+beta2)] calculated. Finally, the compound action potential of the tail nerve was also recorded (using two pairs of needle electrodes for stimulation and recording) and its amplitude and latency (for calculating conduction velocity on the basis of electrode distance) measured. All these records were repeated every 20 minutes. After at least four control sessions, one of the metals was administered via a peritoneal cannula (see Table

Table 1 Doses of lead, mercury and manganese given to rats. The metal salts were dissolved in distilled water and injected intraperitoneally. Alcohol-pretreated rats received only the low dose. Parallel control rats received distilled water. Each group counted eight rats.

Metal	Dose	Pure metal / mg kg ⁻¹
LEAD	high dose	1000
	low dose	500
	low dose + alcohol	500
MERCURY	high dose	7.0
	low dose	3.5
	low dose + alcohol	3.5
MANGANESE	high dose	50
	low dose	25
	low dose + alcohol	25

1 for the doses) and further 8 recording sessions (up to 160 min after administration) were carried out. Alcohol-pretreated rats received only the lower metal doses. Another group of non-pretreated rats received the same amount of distilled water and served as parallel controls.

To eliminate individual variations in absolute measured values of parameters (amplitude, latency and ECoG index), data of each animal were expressed in relative values, taking as the unit the average of the four pre-administration measurements. Of these individual relative data (now plain numbers with no unit of measure), group mean was calculated for each time point and plotted against time (see Figures). The difference between the treated rats and the parallel controls was observed as difference in the time trend. Its statistical significance was tested by

one-way ANOVA with post hoc LSD and $p < 0.05$ was considered significant.

RESULTS

Acute metal administration caused a shift to lower frequencies in the spontaneous cortical activity. The corresponding change in the "ECoG index" was slight and remained below significance except in rats receiving high-dose Hg^{2+} . Alcohol pretreatment had no noteworthy effect on this parameter.

The amplitude of the somatosensory EP increased after administration of the metals. Compared to the pre-administration control period, the effect was very strong with high-dose Hg^{2+} , moderate with high-dose Pb^{2+} , and quite weak with Mn^{2+} (Figure 1). Figure 1

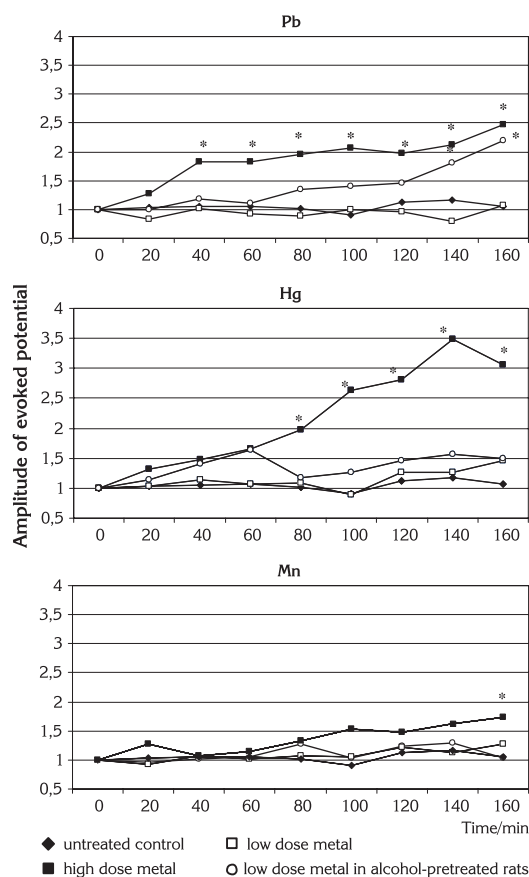


Figure 1 The effect of the three heavy metals on the amplitude of the somatosensory cortical evoked potential. Abscissa: time after ip administration of the metal (in the 0th min). Ordinate: relative change, compared to the average of the pre-administration period (=1). Means, n=8. * $p < 0.05$ vs. control (ANOVA).

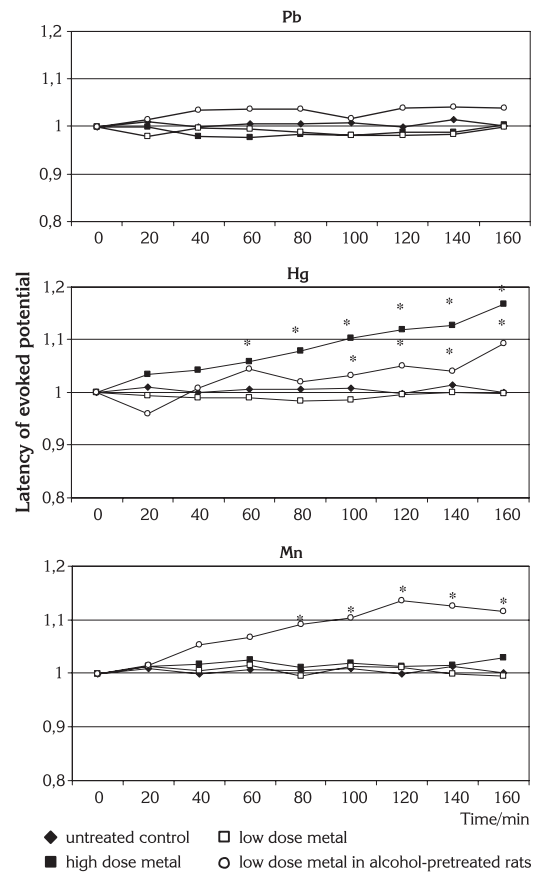


Figure 2 The effect of the three heavy metals on the first peak latency of the somatosensory cortical evoked potential. Abscissa: time after ip administration of the metal (in the 0th min). Ordinate: relative change, compared to the average of the pre-administration period (=1). Means, n=8. * $p < 0.05$ vs. control (ANOVA).

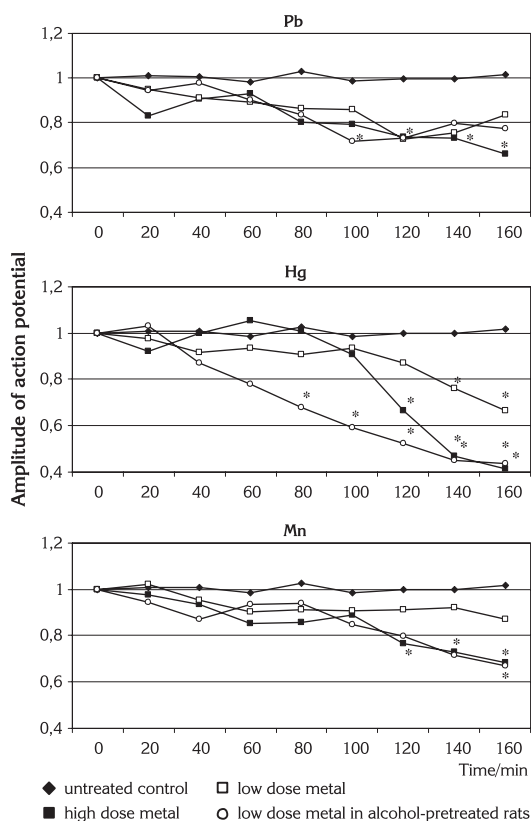


Figure 3 The effect of the three heavy metals on the amplitude of the tail nerve compound action potential. Abscissa: time after ip administration of the metal (in the 0th min). Ordinate: relative change, compared to the average of the pre-administration period (=1). Means, n=8. *p<0.05 vs. control (ANOVA).

also shows that the effect of the three metals had dissimilar time courses and became significant after different times following administration. The effect of the low doses was minimal and was potentiated by alcohol only in case of Pb²⁺ (Figure 1).

In the Pb²⁺-treated rats, the latency of the first peak of EP remained practically unchanged (Figure 2). With high-dose Hg²⁺ and Mn²⁺, a gradually evolving, significant increase in the latency was seen, while the effect of the low doses was negligible. In alcohol-pretreated rats, the effect of low-dose Hg²⁺ was significant, but the effect of low-dose Mn²⁺ remained unchanged.

Both parameters of the tail nerve compound action potential, that is, amplitude (Figure 3) and conduction velocity (Figure 4), were decreased by the administered metals. On this type of nervous activity, the low dose of the metals also had an effect. In alcohol-pretreated rats, the effect of low-dose Pb²⁺ was

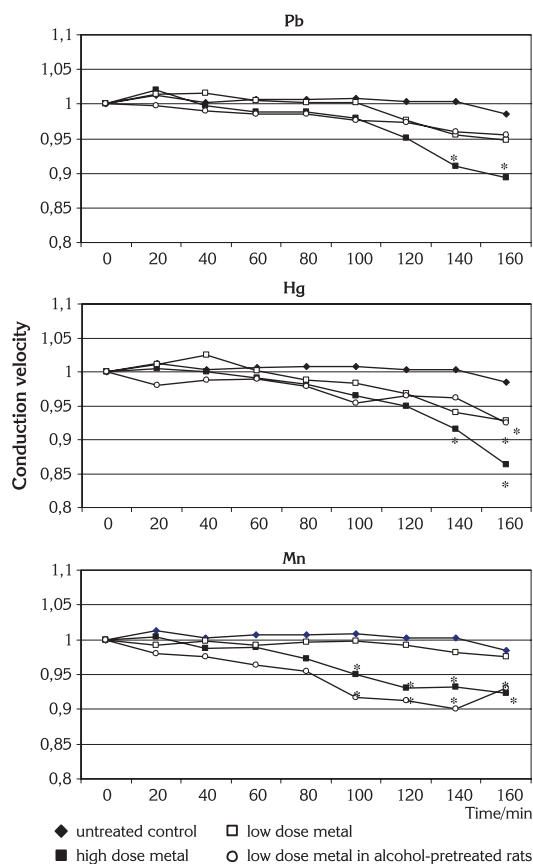


Figure 4 The effect of the three heavy metals on the conduction velocity of the tail nerve. Abscissa: time after ip administration of the metal (in the 0th min). Ordinate: relative change, compared to the average of the pre-administration period (=1). Means, n=8. *p<0.05 vs. control (ANOVA).

not different, but the effect of low-dose Hg²⁺ on the amplitude, and of low-dose Mn²⁺ on both parameters was potentiated.

DISCUSSION

In the evaluation of central nervous effects obtained by experimental metal application, internal exposure (the access of the metal ions to the brain) is crucial. Intraperitoneally injected Pb²⁺, in spite of the poorly soluble salt possibly formed with the physiological Cl⁻ anions, is readily absorbed and passes the blood-brain barrier above the concentration threshold (31). In case of high blood lead level, the barrier itself is damaged (32). Hg²⁺ has a low initial penetration rate across the blood-brain barrier (33). The barrier, however, is also

damaged shortly after the administration of mercury (34). The transport of Mn^{2+} is most likely of facilitated type (35), and rapid enough to induce effects within two hours.

Increased fluidity of nerve cell membranes after ethanol treatment was described by *Edelfors and Ravn-Jonsen* (36). The resulting increase of the permeability of the blood-brain barrier (37) may permit more metal ions to reach the brain.

The effect of Pb^{2+} , Hg^{2+} and Mn^{2+} on the spontaneous cortical activity was qualitatively similar. In case of Hg^{2+} (the only metal with significant effect on the ECoG), an impact on the ascending cholinergic activation (38) is likely. Inorganic mercury is known to inhibit choline acetyltransferase (39). It also decreases the binding of acetylcholine (ACh) to the muscarinic receptors (40), diminishing thereby the activation of the cortex. Pb^{2+} also could interfere with the ascending cholinergic activation of the cortex by increasing the spontaneous and decreasing the stimulus-evoked synaptic release of ACh (41). In alcoholic humans, increased EEG synchronization is typical, possibly indicating the involvement of GABAergic and/or glutamatergic transmission (42). This could account for the synergism between the metals and alcohol on the ECoG, but this was seen only with Hg^{2+} and Mn^{2+} in our study.

As to EP parameters, one possible mechanism of amplitude increase is the general interrelationship with spontaneous activity. In case the latter has slowed or decreased, the amplitude of evoked responses generally increases both in animals (43) and humans (44). The effect of the metals on the glutamatergic thalamocortical input may also contribute to the amplitude increase. The uptake of glutamate into the astrocytes is inhibited by Hg^{2+} (45) and Mn^{2+} (46). In hippocampal neurons *in vitro*, Pb^{2+} diminished the stimulus-evoked release of glutamate and GABA (47) by a Ca^{2+} -dependent mechanism partly similar to that found by *Suszkiw et al.* (41) in rat brain synaptosomes.

Mitochondrial complex II (48), and complex III (49) were found to be inhibited by Mn^{2+} . Insufficient energy production in the neurons can reduce axonal conduction velocity, first of all in the fast, myelinated fibers producing the major part of the compound peripheral action potential recorded in our study. In the cortex, reduced energy supply decreases spontaneous activity, leading to the preponderance of slow waves.

The effect of Hg^{2+} and Pb^{2+} on the peripheral nerve conduction probably results from the blockade

of voltage-dependent Ca^{2+} -channels (50). Mn^{2+} has the same effect (51) and can further impede impulse propagation by causing energy insufficiency (see above).

The present results point to the possible synergistic effect of alcohol and heavy metals on the nervous system in rats. In humans with similar exposure, such as the workforce in smelters and metal-processing plants, alcohol consumption can aggravate the known neurotoxic effects of metals.

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Sažetak**AKUTNI UČINCI OLOVA, ŽIVE I MANGANA U KOMBINACIJI S ALKOHOLOM NA SREDIŠNJI I PERIFERNI ŽIVČANI SUSTAV U ŠTAKORA**

Teški metali, zbog velike primjene u industrijskim procesima, kao agrokemikalije i u predmetima za domaćinstvo, mogu uzrokovati vrlo opsežno onečišćenje i mogu se naći u raznim uzorcima hrane. Jedan od ciljnih organa za metale je središnji živčani sustav. Toksični efekti teških metala mogu biti izmijenjeni utjecajem čimbenika povezanih s načinom života, kao što je konzumiranje alkoholnih pića. Svrha je ovog rada istražiti promjene spontane kortikalne aktivnosti (ECoG), potencijale izazvane osjetljivošću korteksa (EP) i potencijale aktivnosti perifernih živaca. Ispitivanja su provedena na štakorima koji su prethodno tretirani alkoholom i zatim intraperitonealno teškim metalima kao što su olovo, živa i mangan. Živa izaziva smanjenje ECoG, dok mangan i olovo slabije djeluju, a prethodni tretman alkoholom minimalno mijenja učinak. Amplituda EP povećana je pod djelovanjem metala. Utjecaj žive je najjači, a olova najslabiji, ali oba su efekta pojačana alkoholom. Konzumiranje alkohola može pogoršati poznate neurotoksične efekte pri izlaganju teškim metalima.

KLJUČNE RIJEČI: *kortikalna aktivnost, nastali potencijali, neurotoksičnost, periferna aktivnost, teški metali*

REQUESTS FOR REPRINTS:

András PAPP
Department of Public Health, University of Szeged
Dóm tér 10, H-6720 Szeged, Hungary
E-mail: ppp@puhe.szote.u-szeged.hu