NEUROTOXICITY OF LEAD AND MERCURY IN ACUTE EXPOSURE

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Abstract:

The use of heavy metals can lead to considerable emission and, hence, harmful levels at workplaces - affecting employees - and in the general environment - resulting in airborne, foodborne etc. population exposure. Lead and mercury represent an environmental health hazard including nervous system damages. Beyond human studies on exposed individuals, animal experimentation is required in order to elucidate toxic mechanisms and develop biomarkers for early detection of the adverse effects.

The aim of this study was to see the short-term effect of inorganic lead and mercury on the activity of the somatosensory system of rats. Weak electric shocks to the whiskers served as stimuli, and the evoked nervous activity was recorded from the cortical and subcortical focus of the brain. From the cortex, spontaneous activity was also recorded. Both lead and mercury caused alterations in the recorded stimulus-evoked and spontaneous bioelectric activity. These alterations probably reflect a specific action of the heavy metals on the nervous system so they have a potential use in human health protection.

Keywords:

lead, mercury, environment, neurotoxicity, rat

1. INTRODUCTION

A number of heavy metals are known to affect the activity of the nervous system of animals and humans, as indicated by the multitude of neurological signs following occupational exposure, or by the effects of airborne, foodborne etc. exposure of the population.

Lead has been used in large amounts in metal and inorganic forms (in batteries, piping, paints, solders etc), and tetraethyl lead was, and in a number of counties still is, used as a petrol additive. Lead in any form is accumulated in the central nervous system, first of all in the cortex and hippocampus [15]. Pb^{2+} interferes with Ca-dependent regulation of protein kinase C, calmodulin, ATPases, etc. due to the competition of with Ca^{2+} ions [3,27]. Partly due to the interference with Ca^{2+}, lead also affects several transmitter systems. GABA uptake was decreased and dopamine uptake increased in synaptosomes from lead-treated rat brains [16]. Alterations in the dopaminergic, cholinergic and glutamatergic control of behavior were observed in lead-treated animals [10]. In humans, alterations of various forms of central and peripheral evoked activity, like sensory evoked potentials and nerve conduction

velocity, were described in lead-exposed individuals [2,19]. In our earlier studies, similar changes were found in rats after up to 12 weeks oral exposure by Pb^{2+} [22].

Mercury is another heavy metals known to be harmful for the nervous system. In occupational exposure to inorganic mercury, alterations of the spontaneous [25] and stimulus-evoked [19] cortical electrical activity have been reported. Mercury in animal experiments affected a number of ion channels in the peripheral and central nervous system [29]. Hg^{2+} also interfered with calcium homeostasis, by disturbing Ca uptake to the endoplasmic reticulum [13]. In rats treated with ionic mercury, higher than normal levels of the transmitters noradrenaline [14] as well as dopamine and serotonin [18] were seen. In vitro ligand binding of rat cortical muscarinic receptors also was negatively affected by Hg^{2+} [8]. In earlier studies of our group on mercury effects on the cortical activity, rats receiving subchronic $HgCl_2$ treatment showed alterations in the spontaneous [11] and stimulus evoked [28] cortical activity.

The aim of the present study was to see the short-term effect of inorganic lead and mercury on the activity of the somatosensory system of rats.

2. METHODS

Adult male Wistar rats of ca. 350 g b.w. were used in the experiments. After urethane anaesthesia (1000 mg/kg b.w., ip.) the animals' head was fixed in a stereotaxic frame and the left hemisphere was exposed. Wounds were sprayed with 10 % lidocaine and the exposed cortex was covered with warm paraffin oil. Recording of spontaneous activity (electrocorticogram, ECoG) and evoked potentials (EPs) commenced after an hour of recovery. Somatosensory stimulation was done by a pair of needles delivering weak electric shocks to the whiskery part of the skin (rectangular pulses: 3-4 V, 0.2 msec). EPs were recorded from the primary somatosensory cortical focus (ball-tipped silver electrode) and from the thalamic relay nucleus VPM (steel needle electrode placed to stereotaxic coordinates [24]. The pattern of recording consisted of a five minutes ECoG taken from the cortical sufrace, then EPs by applying one train of 20 stimuli to the whiskery skin. This pattern was repeated every 20 minutes.

Recording and evaluation of the electrical activity was done by a PC and the NEUROSYS software (Experimetria, UK). After 5 control records, mercury ($HgCl_2$, 7 mg/kg) or lead ($Pb(CH_3COO)_2$, 1000 mg/kg) was administered via a peritoneal cannula and the recording was continued for further ca. 2 hours. After averaging the individual EPs, peak-to-peak amplitude and latency of the main peaks (from the stimulus artefact) was measured. From the ECoGs, band activity (standard, delta to gamma [17] was automatically determined and the so-called ECoG index calculated (relation of the low and high frequencies in the recorded ECoG; delta+theta/beta1+beta2).

3. RESULTS

The effect of the heavy metals mostly started immediately after administration and developed in the next 2 hours.

On the spontaneous activity (ECoG index), a trend to decreased activity was seen (Fig. 1). The effect was significant when Hg, but not when Pb, was administered.

The amplitude of the evoked potentials increased. This effect was also stronger with Hg than with Pb, and was generally more pronounced on the cortical

projection area than at the thalamic relay site (Fig. 2). Both metals increased the latency of the EPs (Fig. 3), the effect being significant both at the thalamic and at the cortical recording site.

In case of Hg administration, there was a significant correlation between the alteration of the spontaneous cortical activity (ECoG index) and the evoked potential amplitude, as shown by the correlation diagram (Fig. 4, left). In case of Pb, the correlation was poor (Fig. 4, right).

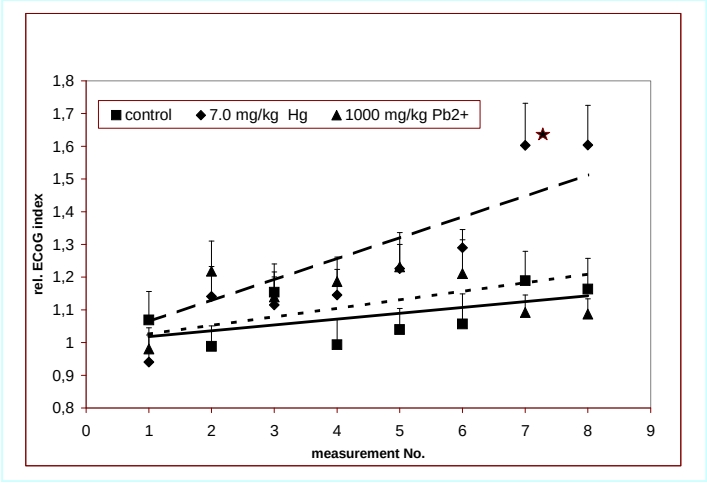

Fig. 1. *Effect of Hg and Pb on the spontaneous cortical activity of rats (mean+SD, n=8).*
Abscissa: measurements (metal given just before measurement 1).
Ordinate: relative change of the ECoG index (treated/averaged control).
*Linear trend lines fitted by EXCEL. *: p<0.05*

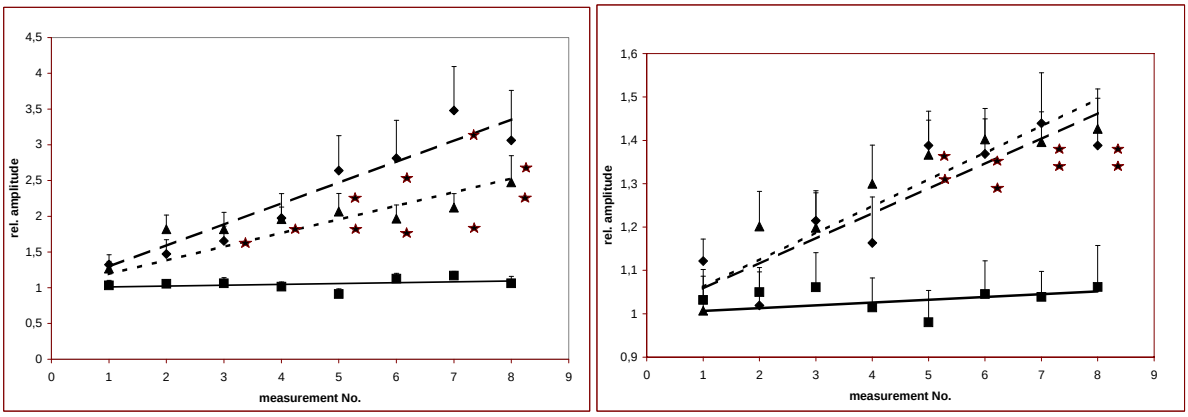

Fig. 2. *Increase of the evoked potential amplitude on Hg and Pb administration in the cortical focus (left) and the thalamic relay site (right). Displayed as in Fig. 1.*

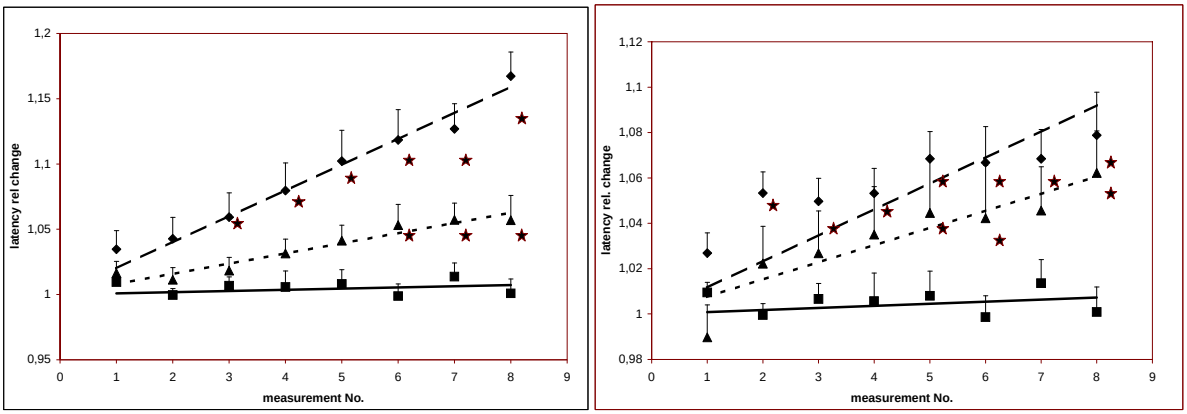

Fig. 3. *Increase of the evoked potential latency (1st peak) on Hg and Pb administration in the cortical focus (left) and the thalamic relay site (right). Displayed as in Fig. 1.*

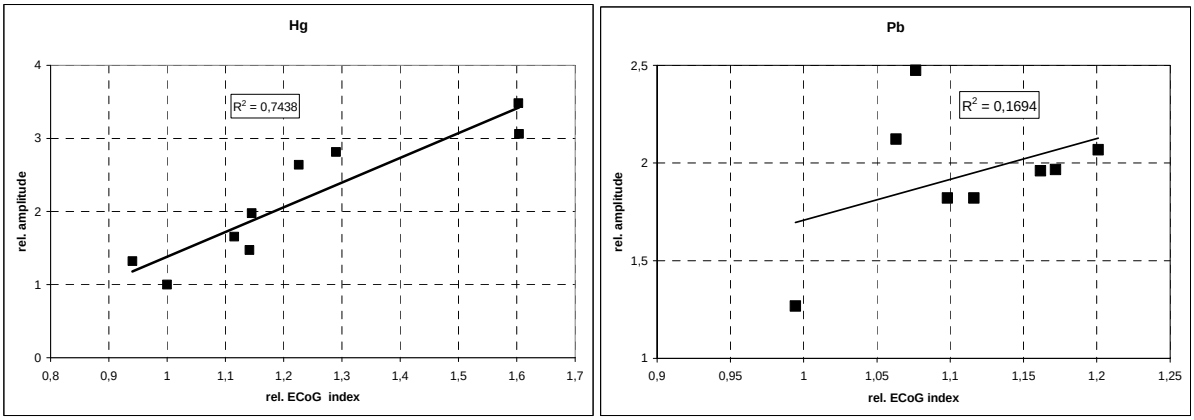

Fig. 4*. Diagrams of the correlation between the changes of the spontaneous (abscissa) and the evoked (ordinate) cortical activity in case of Hg (left) and Pb (right). trend lines fitted and correlation coefficients calculated by EXCEL.*

4. DISCUSSION

Following exposure to inorganic mercury compounds, accumulation of mercury within the CNS has been demonstrated [1,21], in spite of its tendency to bond to plasma proteins. Pb^{2+}, although forms low solubility salts with physiological anions like Cl^-, is readily absorbed by various routes of exposure [31]. Entering the blood stream, Pb^{2+} passes the blood-brain barrier above a concentration threshold [4].

The alterations of the cortical evoked potentials found in our work (increased latency and amplitude) were similar to those seen in chloralkali workers [9] which has several possible explanations. The excitatory thalamocortical input is glutamatergic, and Hg^{2+} inhibits the glial uptake of Glu [7]. Lead, too, interferes with the spontaneous and stimulus-evoked release of Glu and GABA [5,6,30]. In case of Hg^{2+}, an effect on the ascending cholinergic activation [20] is also likely. Hg^{2+} inhibits choline acetyltransferase [12] and decreases the binding of ACh on the muscarinic receptors [26], resulting in less activation. Inorganic lead could possibly interfere with the cholinergic activation of the cortex by increasing the spontaneous and decreasing the

stimulus-evoked synaptic release of ACh [30]. In our results, however, the correlation between spontaneous and evoked cortical activity was firm for Hg^{2+} but poor for Pb^{2+}.

These alterations probably reflect a specific action of the heavy metals on the nervous system so they have a potential use in human health protection.

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5. REFERENCES

1. *Aposhian, M.M., Maiorino, R.M., Xu, Z., Aposhian, H.V.: Sodium 2,3-dimercapto-1-propanesulfinate (DMPS) treatment does not redistribute lead or mercury to the brain of rats. Toxicology 109:49-55 (1996).*
2. *Araki, S., Sato, H., Yokoyama, K., Murata, K.: Sublcinical neurophysiological effects of lead: A review on peripheral, central, and autonomic nervous system effects in lead workers. Am. J. Ind. Med. 37:193-204 (2000).*
3. *Bettaiya, R., Yallapragada, P.R., Hall, E., Rajana, S.: In vitro effect of lead on Ca2+-ATPase in synaptic plasma membranes and microsomes of rat cerebellar cortex and cerebellum. Ecotoxicol. Environ. Safety 33:157-62 (1996).*
4. *Bradbury, M.W. Deane, R.: Permeability of the blood-brain barrier to lead. NeuroToxicol. 14:131-136 (1993).*
5. *Braga, M.F.M., Pereira, E.F.R., Albuquerque, E.X.: Nanomolar concentrations of lead inhibit glutamatergic and GABAergic transmission in hippocampal neurons. Brain Res. 826:22-34 (1999a).*
6. *Braga, M.F.M., Pereira, E.F.R., Marchioro, M., Albuquerque, E.X.: Lead increases tetrodotoxin-insensitive spontaneous release of glutamate and GABA from hippocampal neurons. Brain Res. 826:10-21 (1999b).*
7. *Brookes, N.: In vivo evidence for the role of glutamate in the CNS toxicity of mercury. Toxicology 76:245-256 (1992).*
8. *Castoldi, A.F., Candura, S.M., Costa, F., Manzo, L., Costa, L.G.,: Interaction of mercury compounds with muscarinic receptor subtypes in the rat brain. NeuroToxicol. 17:735-741 (1996).*
9. *Chang, Y.C., Yeh, C.Y., Wang, J.D.: Subclinical neurotoxicity of mercury vapor revealed by a multimodality evoked potential study of chloralkali workers. Am. J. Ind. Med. 27:271-279 (1995).*
10. *Cory-Schlechta, D.A.: Relationships between lad-induced learning impairments and changes in dopaminergic, cholinergic and glutamatergic neurotransmitter system functions. Ann. Rev. Pharmacol. Toxicol. 35:391-415 (1995).*
11. *Dési, I., Nagymajtényi, L., Schulz, H.: Effect of subchronic mercury exposure on electrocorticogram of rats. NeuroToxicol. 17:719-724 (1996).*
12. *Dwivedi, C., Raghunathan, R., Joshi, B.C., Foster, H.W.: Effect of mercury compounds on acetylcholin transferase. Res. Commun. Chem. Pathol. Pharmacol. 30:381-384 (1980).*
13. *Freitas, A.J., Rocha, J.B.T., Wolosker, H., Souza, D.O.G.: Effects of Hg^{2+} and CH_3Hg^{+} on Ca^{2+} fluxes in rat brain synptosomes, Brain Res. 738:257-264 (1996).*
14. *Gasso, S., Sunol, C., Sanfeliu, C., Rodriguez-Farre, E., Cristofol, R.M.: Pharmacological characterization of the effects of methylmercury and mercuric chloride on spontaneous noradrenaline release from rat hippocampal slices. Life Sci. 67:1219-1231 (2000).*

15. *Grandjean, P.: Regional distribution of lead in human brains. Toxicology 2:65-69 (1978).*
16. *Jablonska, L., Walski, M., Rafalowska, U.: Lead as an inductor of some morphological and functional changes in synaptosomes from rat brain. Cell. Mol. Neurobiol. 14:701-707 (1994).*
17. *Kandel, E.R., Schwartz, J.H.: Principles of Neural Science. Elsevier, New York, pp.643-644 (1985).*
18. *Lamm, O., Pratt, H.: Subclinical effects of exposure to inorganic mercury revealed by somatosensory-evoked potentials, Eur. Neurol. 24:237-243 (1985).*
19. *Lille, F., Hazemann, P., Garnier, R., Dally, S.: Effects of lead and mercury intoxications on evoked potentials. J. Toxicol. Clin. Toxicol. 26:103-116 (1988).*
20. *Metherate, R., Cox, C.L., Ashe, J.H.: Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. J. Neurosci. 12:4701-4711 (1992).*
21. *Möller-Madsen, B.: Localization of mercury in CNS of the rat. II. Intraperitoneal injection of methylmercuric chloride (CH_3HgCl) and mercuric chloride ($HgCl_2$). Toxicol. Appl. Pharmacol. 103:303-323 (1990).*
22. *Nagymajtényi, L., Schulz, H., Papp, A., Dési, I.: Behavioural and electophysiological changes caused by subchronic lead exposure in rats. Centr. Eur. J. Occup. Environ. Med. 3:195-209 (1997).*
23. *Papp, A., Vezér, T., Nagymajtényi, L.: Possible functional biomarkers among the properties of cortical sensory evoked potentials of rats treated with xenobiotics. J. Physiol. 526:161p. (2000).*
24. *Paxinos, G., Watson, C.: The rat brain in stereotaxic coordinates. Academic Press, New York, (1982).*
25. *Piikivi, L. Tolonen, U.: EEG findings in chloralkali workers subjected to low long term exposure to mercury vapour. Br. J. Ind. Med. 46:370-375 (1989).*
26. *Rajanna, B., Chetty, C.S., Rajanna, S., Hall, E., Fail, S., Yallapragada, P.R.: Interaction of metals with muscarinic cholinoceptor and adrenoceptor binding, and agonist-stimulated inositol phospholipid hydrolysis in rat brain. Comp. Biochem. Physiol. 116C:111-116 (1997).*
27. *Sandhir, R., Gill, K.D.: Alterations in calcium homeostasis on lead exposure n rat synaptosomes. Mol. Cell. Biochem. 131:25-33 (1993).*
28. *Schulz, H., Nagymajtényi, L., Papp, A., Dési, I.: Behavioural and neurophysiological consequences of subchronic mercury exposure in rats. Centr. Eur. J. Occup. Environ. Med. 3:210-223 (1997).*
29. *Sirois, Y.E., Atchison, W.D.: Effects of mercurials on ligand- and voltage-gated ion channels: A review. NeuroToxicol. 17:63-84 (1996).*
30. *Suszkiw, J., Toth, G., Murawsky, M., Cooper, G.P.: Effects of Pb^{2+} and Cd^{2+} on acetylcholine release and Ca^{2+} movements in synaptosomes and subcellular fractions from rat brain and torpedo electric organ. Brain Res. 323:31-46 (1984).*
31. *WHO: Lead. Environmental Health Criteria 3. WHO, Geneva, (1977).*