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Effect of manganese on neural endocrine hormones in serum of welders and smelters

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ABSTRACT

Background: Although manganese (Mn)-induced neurotoxicity effects are well known among occupational Mn exposure, few reports have investigated the effects on endocrine systems among welders and smelters.
Objective: To determine the effect of high level occupational manganese (Mn) exposure on neuropsychological parameters and hormonal status.
Methods: We used a cross-sectional design with 52 welders, 48 smelters and 43 age-matched office workers from the same factory in China. We analyzed serum endocrine hormones level and airborne Mn concentrations. Erythrocyte and urine Mn levels were quantified using inductively-coupled plasma atomic emission spectroscopy.
Results: The geometric mean of air Mn concentrations for the welders and smelters were 19.7 and 273.1 μg/m^3, respectively. Mn concentrations in erythrocytes of smelters were markedly greater than those in controls and welders, but there was no difference between the erythrocytes Mn levels of Control and welders. We also found an increase of Mn levels in the urine of both welders and smelters vs. controls; Mn levels in urine of smelters were higher than in welders. Self-reported neurobehavioral symptoms were higher in welders and smelters than in controls. Finally, thyroid-stimulating hormone (TSH) levels of welders were significantly lower than in controls, whereas smelters had lower prolactin (PRL), testosterone (TST) and follicle-stimulating hormone (FSH) concentrations than either controls or welders.
Conclusions: These results show that smelters have higher Mn exposure than do welders, and that Mn levels in erythrocytes or urine can be a marker for exposure. Moreover, high level occupational Mn exposure increases adverse neurobehavioral effects, and also may disrupt endocrine systems.

1. Introduction

Manganese (Mn) is widely used for production of steel, welding rods, various Mn chemicals, glasses and dry cell batteries [1]. Occupational Mn exposure from professions such as mining [2], smelting, and welding [3] may present an increased risk for neurobehavioral impairment due to brain Mn accumulation and/or secondary peripheral effects. An extreme case of neurotoxicity induced by Mn is known as manganism, a severe disorder of the central nervous system (CNS) characterized by movement disturbances and psychiatric features, the former of which may resemble Parkinson's disease [4]. Manganism has long been linked to occupational intoxication, especially with miners or welders inhaling high concentrations of Mn dust. The general population also is exposed to Mn from industrial air pollutants, fungicides and pesticides, combustion products of coal-burning plants and motor engines, and contrast agents used for magnetic resonance imaging [5,6].

It is well known that dopamine (DA) systems can be an important target for Mn neurotoxicity [7]. In vivo studies have confirmed that nigrostriatal dopamine neurons are one of the main targets for manganese neurotoxicity [8].It is known that dopamine directly modulates prolactin (PRL) secretion via inhibitory D_2 receptors on pituitary lactotrophs, and thus can reflect indirectly the function of hypothalamic

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dopamine secretion [9].There are, however, contradictory results about how Mn affects PRL levels. An early study reported higher serum PRL levels and higher urine and blood Mn levels in workers in an environment where Mn levels were lower than the allowable time-weighted average [10]. Similarly, Alessio et al. [11] found an increase of serum PRL among 14 male workers from a foundry producing ferrous-manganese alloys, and partial correlation analysis results showed a close relationship between serum PRL and Mn levels in whole blood and urine [10,12]. Similar data were found in another study [13], and together these results might suggest damage to tuberoinfundibular dopamine neurons that decreases portal dopamine release, disinhibiting PRL secretion. In contrast, Wang et al. [14]reported that long-term low levels Mn exposure actually decreased the serum PRL levels, whereas Roels et al. [15] found no change in serum PRL levels of workers employed in a plant producing dry alkaline batteries factory. A plausible explanation for these contradictory results may be the nature of the occupational exposure, for example as influenced by the form of the Mn, other concomitant metals, and the temporal pattern of exposure.

For these reasons, we sought to determine how occupational Mn exposure from different professions affected neuroendocrine and physiological function. Welders and smelters are the most prevalent working populations exposed to Mn, and are exposed to different environmental Mn doses [3]. Thus, we chose to study welders, smelters, and age-matched office workers from the same factory in China to evaluate these effects.

2. Methods and materials

2.1. Procedures

All of the workers gave their written informed consent prior to examination. The study was conducted in accordance with the principles for medical research involving human subjects as defined by the Declaration of Helsinki, and with a study protocol approved by the Ethics Committee of the Guangxi Medical University. Each participant signed informed consent forms approved by the Guangxi Medical University's Institutional Review Board, and thereby agreed to use of their clinical data from their worker's compensation evaluation that included Health Insurance Portability and Accountability Act consents. All data were double-entered using Epi Data software to assure accuracy. Blood and urine were collected after shifts, and information about the workplaces, smoking habits, and the medical history were documented in a questionnaire. Erythrocyte and urine samples were collected on the same day as air sampling.

2.2. Study populations

All participants in this study were male with mean age of 33.7 years. Forty-eight smelters who have been regularly engaged in the daily smelt with a high level of Mn exposure were recruited from iron alloy smelting factory in Guangxi. Fifty-two welders regularly engaged in daily welding with a lower level of Mn exposure were selected from a construction machinery manufacturing company in Guangxi. The unexposed control group consisted of 43 office workers who were selected from a company in the same city, and who had no history of occupational exposure to Mn and other metals. None of the study subjects reported exposure to other toxic substances or radiation therapy, or were substance abusers; all of the latter may cause neurotoxicity, and/or effects on reproductive and endocrine systems. No subject had neurologic, reproductive, or endocrine system disease.

2.3. Criteria for participation in the study

The Mn-exposed workers had to have a minimum of one year of relevant work history. The controls could have no reported exposure to Mn or other neurotoxic substances. No subject could have liver or kidney disease, nor a history of current or past diseases of the CNS (e.g., schizophrenia, Parkinson's disease, multiple sclerosis, etc.). Other exclusion criteria included prior exposure to other neurotoxic substances (e.g., Pb or Hg), drug or alcohol abuse, diabetes mellitus, reproductive abnormalities and/or endocrine disorders, or for Controls, prior employment at a workplace that had exposure to known neurotoxic substances.

2.4. Questionnaire design

In this study, workers answered a self-administered questionnaire according to our previous studies [16,17] to assess their personal information and neurobehavioral symptoms. The questionnaire consisted of two parts. The personal information including occupational history, lifestyle, and family and medical history from which toxic or cofounding factors can be deduced. The neurobehavioral section focused on neurologic, psychiatric, and autonomic symptoms such as dizziness, walking heavily, headache, myasthenia of limbs, unsteady gait, fatigue, difficulty in reading understanding from newspapers or books, sleep disorder, hypomnesia, apathia, aprosexia, increased salivation, tremors, palpitations, hyperhidrosis, numbness, hypaphrodisia, and the like. In order to reduce questionnaire bias, the questionnaires were taken by using one-on-one face-to-face survey forms. The data from the questionnaires was double-entered, and validated by two investigators.

2.5. Air sample collection and analysis

All ambient air samples were collected on mixed cellulose ester membrane filters with a pore size of 0.8 μm and a diameter of 40 mm using personal air samplers (BFC-35, Kejie Instrument Corp., Jintan, China). Sampling was done once every hour for 4 min at a flow rate of 5 L/min, three times per day. Samples of Mn particulates collected on cellulose filters were dissolved in mixed acid (1:9 $HClO_4$:HNO_3), and diluted with 1% HNO_3. Mn levels in the samples were quantified by atomic absorption spectrophotometry (AAS, AA6800, Shimadzu, Kyoto, Japan) using the method described in GBZ/T160.13-2004 [18]. As noted above, erythrocyte and urine samples were collected on the same day as air sampling.

2.6. Determination of Mn levels in erythrocytes and urine

The blood was collected by venipuncture of the antecubital vein, and put in anticoagulation (heparin sodium) tubes. Erythrocytes were separated from whole blood, and stored at -80℃ for determination of Mn levels. The urine samples of the workers were collected, 100 μL of concentrated HCl added, and the samples stored at 4℃. Briefly, blood and urine samples were digested with 3 mL mixed acid (concentrated HNO_3/H_2SO_4/HClO4 (v: v: v) = 9:1:1) overnight. Subsequent digestion was conducted on a low-temperature electric hot plate until the solution became transparent. Then the samples were adjusted to 5 mL with double-distilled water. The levels of Mn were measured by using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES, IRIS-2, Themo Jarrel Ash Company, USA) as described previously [19]. The setup of the instrumental conditions was: λ = 257.610 nm; radio-frequency (RF) generator power = 1200 w; analysis pump speed = 100 r/min; washing speed = 100 r/min; atomization airflow = 1.3 L/min; auxiliary gasflow = 1.0 L/min; long wave = 5 s; and short wave = 15 s; Sample rinse time was 30 s, and the maximum integration time was 10 s. The standard curves were established using freshly made metal standards (National standard sample No.GSB 04-1736-2004) on the day of analysis. Mn recovery rate was 95% in erythrocytes and 98.3% in urine, with precision higher than 95.5%. The average limit of detection of this method using for determination of Mn was 0.4 μg/L. All samples were determined three times, and all values were above the limit of detection(LOD).