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TIME SEQUENCE OF OXIDATIVE STRESS IN NEURODEGENERATIVE BRAIN AFTER LONG-TERM LEAD EXPOSURE IN RATS

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Introduction A large number of studies have shown that the developmental neurotoxicity induced by lead is related to oxidative injury, meanwhile, oxidative stress is among the most common mechanisms of neurodegeneration. However, few studies have explored the role of oxidative stress in age-related cognitive impairment caused by prolonged lead exposure and oxidative stress.

Methods In the present study, rats were exposed to low-level lead from the embryonic stage to old age. Dynamic changes in neurodegeneration, endoplasmic reticulum (ER) stress, and oxidative stress in brains during postnatal weeks 3, 41 and 70 (PNW3, PNW41 and PNW70, respectively) were investigated.

Results Lead exposure resulted in neurodegeneration in PNW70 rats based on magnetic resonance imaging (MRI) scans and thionine stain analysis. Amyloid precursor protein (APP) and tau mRNA expression in PNW41 and PNW70 brains increased in a time- and dose-dependent manner. APP and Tau protein levels significantly increased with lead exposure at PNW3 and PNW70. Mechanistically, the expression of the ER stress protein glucose-regulated protein 78 (GRP78) was higher in the presence of lead than in normal controls, which was associated with high levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in brain tissues after lead exposure in PNW3 and PNW70, their changes were like as APP and tau protein that were a u- or j-shaped curve with time of lead exposure.

Conclusion Our findings suggest that the neurodegenerative injuries induced by lead exposure may be mediated by ER and oxidative stresses, and there is a critical period for prevention or intervention AD in early life and later life, however middle-aged people at the latent stage of neurodegenerative process should not be ignored.

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COMBINED EXPOSURE TO LEAD, CADMIUM, ARSENIC, AND MERCURY ALTERS SYNAPTIC HOMEOSTASIS THROUGH SNK-SPAR PATHWAY IN NEURONAL CELLS

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Introduction Lead, cadmium, arsenic, and mercury are widely used in industry and among the leading toxic agents detected in the environment. The deleterious effects encountered after exposure to these individual metals in low doses are well documented. However, human exposure to environmental chemicals is most correctly characterised as an exposure to mixtures, and little is known about the combined impact of these metals.

Methods In our study, the combined impacts of these four metal mixtures (MM) in low doses on synaptic homeostasis as well as the related mechanisms were investigated in cultured hippocampal neurons and NGF-differentiated PC12 cells. F-actin staining was used to emerge the structure of dendrites and spines for synaptic morphology analysis. Immunofluorescence and RT-PCR were applied to examine the expressions of serum-inducible kinase (Snk) and spine-associated Rap guanosinetriphosphatase activating protein (SPAR). The plasmids of shRNA-Snk, SPAR-Wt and SPAR-Mut (S1328) were constructed for transfection Assays.

Results MM exposure declined the density and length of dendritic spines, and dendrite branches in dose-effect relationship in hippocampal neurons. And the mushroom and thin spines were decreased. Simultaneously, the Snk expression were up-regulated accompanying with the down-regulation of SPAR expression. Similar to what observed in the hippocampal neurons, the synaptic morphology analysis of NGF-differentiated PC12 cells showed their neurite length and tip end numbers were declined in dose-effect relationship after MM exposure, which accompanied with the up-regulation of Snk and the down-regulation of SPAR. Snk agonist aggravated these impairment, whereas, Snk knockdown and SPAR overexpression attenuated the changes of neurite outgrowth. In addition, SPAR-Mut (S1328) overexpression performed a better reversion than SPAR-Wt overexpression in the changes of neurite outgrowth induced by MM-exposure.

Conclusion These results indicated that combined exposure to low doses MM disturbed the synaptic homeostasis, and Snk-SPAR pathway might be a novel target to prevent MM induced neurotoxicity.

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THE ASSOCIATION OF BLOOD LEAD LEVEL AND RENAL EFFECTS MAY BE MODIFIED BY METALLOTHIONEIN 1A 2A POLYMORPHISMS

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Introduction Lead toxicity plays an important role in public health. It causes multiple organs damage, and nephrotoxicity is included. Metallothionein (MT) is a cysteine-rich, low molecular weight protein with function of heavy metal detoxification. However, study about how the MT1A and MT2A single nucleotide polymorphisms (SNPs) influence the lead nephropathy is relatively scarce. Our aim is to investigate the association of blood lead levels and renal biomarkers in chronic lead exposure, and to study whether the association was influenced by MT1A2A SNPs.

Methods Blood samples were collected from 485 participants during their annual health examination after informed consent letters were obtained. The blood lead level, urinary creatinine, urinary uric acid, and urinary N-acetyl-beta-d-glucosaminidase (NAG) were measured and analysed. DNA was extracted and used for real-time PCR genotyping two MT1A SNPs

(rs11640851 and rs8052394) and two MT2A SNPs (rs10636 and rs28366003). The MT1A2A SNPs combination was divided into 16 groups. Data were treated for descriptive analysis, one-way ANOVA, and multiple linear regressions by SPSS.

Results Urine uric acid had significantly negative association with time-weighted index of cumulative blood lead (TWICL) after adjusting other potential confounders except 16 groups of MT1A2A SNPs combination. Moreover, the association was modified by 16 groups of SNPs combination. For urine uric acid, group 6th and group 12th were more susceptible to lead toxicity, while group 5th was less susceptible to lead toxicity. On the other hand, urinary NAG was positively associated with TWICL no matter whether the 16 groups were adjusted or not.

Conclusion Urinary uric acid and urinary NAG might be considered as proper indicators of lead nephrotoxicity. Moreover, MT1A2A combination 16 groups were modifiers in the relationship between urinary uric acid and TWICL. The group 5th was positive association while group 6th and 12th were negative association with TWICL on urinary uric acid

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BONE EFFECT UNDER CAUSED BY CO-EXPOSURE TO FLUORIDE AND ARSENIC

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Introduction Chronic exposure to combined fluoride and arsenic continue to be a major public health problem worldwide. Although there have been reports in the literature about the toxicity of arsenic and fluoride individually, there is very little known about the combined effects of these two elements. In this study, based on the population and *in vivo*, the aim is to explore the combined bone toxicity of fluorine and arsenic and provides a scientific basis for the mechanism, prevention and control of endemic combined fluorine-arsenic poisoning on bone toxicity.

Methods The population-based study group was selected from people living in fluoride-arsenic polluted areas due to burning coal in China. The total number of participants was 196 to observing the changes in gene and protein expression of PTH/PKA/AP1 signalling pathway. A total of 90 weaned specific pathogen-free SD rats were randomly assigned to a group to explore the role of PTH-cAMP-PKA signalling pathway on bone toxicity of rats exposed to fluoride and arsenic.

Results Fluoride can increase the expression levels of PTH, PKA, and AP1, but arsenic can only affect the expression of AP1; fluoride and arsenic have an interaction on the expression of AP1, c-fos and Runx2. Fluoride exposure can affect the metabolism of collagen and bone resorption, and arsenic exposure main affect bone resorption, fluoride and arsenic co-exposure have a more significant effect on bone resorption.

Conclusion PTH-PKA-AP1 and PTH-cAMP-PKA signalling pathway may play an important role in bone toxicity of fluoride. Arsenic can affect the expression of c-fos and Runx2, thereby affecting the expression of transcription factor AP1, MMP-9, RANKL and Osterix, indirectly involved in fluoride induced bone toxicity. The main sign of bone damage under the exposure level of the study is osteosclerosis and main combined bone toxicity of fluoride and arsenic showed antagonistic effects

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LOW LEVEL URINE ARSENIC CONCENTRATION AND OBSTRUCTIVE PULMONARY DISEASE AMONG U.S. WORKERS

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Introduction Arsenic (As) is a known carcinogen commonly found in drinking water. An emerging body of evidence suggests that exposure to inorganic arsenic may be associated with non-malignant respiratory disease. The aim of this study was to determine whether there is an association between As exposure at levels seen among workers in the United States and prevalence of asthma, emphysema, chronic bronchitis, and respiratory symptoms.

Methods Urinary As was collected from 5365 participants from the combined 2003–2006 National Health and Nutrition Examination Survey (NHANES) cohorts. Two methods to adjust for organic As component were incorporated into the statistical model. Linear and logistic regression models compared urinary As adjusted for organic As with diagnoses of obstructive pulmonary disease and respiratory symptoms.

Results Geometric mean concentration of urinary As were not significantly different between participants with and those without asthma, chronic bronchitis, and emphysema. Odds of having asthma was 0.71 for participants with the highest quintile of urinary As (≥ 17.23 µg/dl) when compared to the lowest quintile (≤ 3.52 µg/dl). A significant association was found between increasing urinary As concentration and decreasing age, male gender, and non-'white' race.

Conclusion A significant association between urinary As and obstructive pulmonary disease and symptoms was not demonstrated in the U.S. working population

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BONE METABOLISM ABNORMALITY AND RENAL DYSFUNCTION IN CADMIUM EXPOSED FARMER FROM THAILAND

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Introduction Paddy fields in Mae Sot, Tak province of Thailand are polluted with cadmium (Cd) over safe level. Farmers exposed Cd from contaminated rice consumption and the high prevalence of kidney dysfunction was shown in the exposed population. Bone fracture is another Cd related pathology which shown in elderly with high exposure level. The identification of high risk individuals will be advantageous to provide suitable health promotion and to prevent severe pathology. This study was done to compare bone fracture risk between glomerular dysfunction, proximal tubular dysfunction and Calcium (Ca) handling abnormality.

Methods Serum osteocalcin and cross-linked N-telopeptide of type I collagen to detect bone metabolism abnormalities, whereas glomerular filtration rate, serum cystatin C, urinary β 2-microglobulin (β 2-MG) and fractional excretion of calcium