1373 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.

1374 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.

171 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 PCRgenotyping two MT1A SNPs