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Internal Mercury Exposure Levels Correlated to DNA Methylation of Imprinting Gene H19 in Human Sperm of Reproductive-Aged Man

Authors : Zhaoxu Lu, Yufeng Ma, Linying Gao, Li Wang, Mei Qiang

Abstract : Mercury (Hg) is a well-recognized environmental pollutant known by its toxicity of development and neurotoxicity, which may result in adverse health outcomes. However, the mechanisms underlying the teratogenic effects of Hg are not well understood. Imprinting genes are emerging regulators for fetal development subject to environmental pollutants impacts. In this study, we examined the association between paternal preconception Hg exposures and the alteration of DNA methylation of imprinting genes in human sperm DNA. A total of 618 men aged from 22 to 59 was recruited from the Reproductive Medicine Clinic of Maternal and Child Care Service Center and the Urologic Surgery Clinic of Shanxi Academy of Medical Sciences during April 2015 and March 2016. Demographic information was collected using questionnaires. Urinary Hg concentrations were measured using a fully-automatic double-channel hydride generation atomic fluorescence spectrometer. And methylation status in the DMRs of imprinting genes H19, Meg3 and Peg3 of sperm DNA were examined by bisulfite pyrosequencing in 243 participants. Spearman's rank and multivariate regression analysis were used for correlation analysis between sperm DNA methylation status of imprinting genes and urinary Hg levels. The median concentration of Hg for participants overall was 9.09μg/l (IQR: 5.54 - 12.52μg/l; range = 0 - 71.35μg/l); no significant difference was found in median concentrations of Hg among various demographic groups ($p > 0.05$). The proportion of samples that a beyond intoxication criterion (10μg/l) for urinary Hg was 42.6%. Spearman's rank correlation analysis indicates a negative correlation between urinary Hg concentrations and average DNA methylation levels in the DMRs of imprinted genes H19 ($rs=-0.330$, $p = 0.000$). However, there was no such a correlation found in genes of Peg3 and Meg3. Further, we analyzed of correlation between methylation level at each CpG site of H19 and Hg level, the results showed that three out of 7 CpG sites on H19 DMR, namely CpG2 ($rs =-0.138$, $p = 0.031$), CpG4 ($rs =-0.369$, $p = 0.000$) and CpG6 ($rs=-0.228$, $p = 0.000$), demonstrated a significant negative correlation between methylation levels and the levels of urinary Hg. After adjusting age, smoking, drinking, intake of aquatic products and education by multivariate regression analysis, the results have shown a similar correlation. In summary, mercury nonoccupational environmental exposure in reproductive-aged men associated with altered DNA methylation outcomes at DMR of imprinting gene H19 in sperm, implicating the susceptibility of the developing sperm for environmental insults.

Keywords : epigenetics, genomic imprinting gene, DNA methylation, mercury, transgenerational effects, sperm
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