A metabolomic study on spermatogenesis failure induced by heavy metal exposome

1.Introduction

Increasing heavy metal pollution may impact spermatogenesis. However, previous research has been limited to a few known toxic metals.

Method

A total of 962 patients with spermatogenesis failure and healthy controls were recruited for the study. ICP-MS was utilized to detect heavy metal exposome in urine, while UPLC-Q Exactive was employed to analyze metabolome of both urine and seminal plasma. Based on the human study, we established in vivo and in vitro exposure models as well as key metabolic reversal models to observe reproductive indicators and analyze downstream molecules.

Results

Among the 52 heavy metals detected, molybdenum was the most significant element related to spermatogenesis failure with the highest content. The metabolome associational study demonstrated the significant association between molybdenum exposure, adenosine metabolism, and spermatogenic disorders. Mice aged 8 and 56 weeks were exposed to molybdenum with increasing detected molybdenum in urine and testis. Pathological examination showed that molybdenum specifically impaired testis tissue. The number of sperm and the proportion of progressive sperm were decreased, while the sperm deformity rate was increased after molybdenum exposure. There was an exacerbation of apoptosis in both spermatocytes and Sertoli cells in the testicles of mice. The gene expression of Nt5e, Adora1, Bax, Caspase-9, Caspase-3, and oxidative glutathione in the testes were increased. The above effects were partially restored by the reversal of adenosine metabolism. Molybdenum exposure also promoted cell apoptosis and lead to an increase in apoptotic gene expression in GC-2 cells, and the effects were restored in the adenosine metabolism reversal group.

Conclusions

This study provided a global understanding of spermatogenesis failure caused by heavy metal exposome, and further clarified a novel toxic pathway as Molybdenum-Nt5e enzyme-Adenosine-Adenosine A1 receptor-Mitochondrial dependent apoptosis-Spermatogenesis failure, providing new information for male reproductive toxicity caused by heavy metal exposure.

Keywords: exposome; metabolome; molybdenum; adenosine metabolism; spermatogenesis failure