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Extended Abstract

Effects of zinc on gene expressions induced by cadmium in prostate and testes of rats

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Human reproductive toxicity and prostate cancer, probably related to cadmium (Cd), have been paid more attention in recent years. In rodent models, the testes and ventral prostate (VP) have shown a higher sensitivity to Cd-induced carcinogenesis than other tissues, but there is no unifying concept that a recognized signal regulates those effects (Waalkes 1992, 1999).

Zinc (Zn) has an important impact on Cd carcinogenesis, including the selective antagonisms of carcinogenic effects of Cd at many different target organs, e.g. lung or testes. The aim of this paper was to explore possible mechanisms responsible for Cd-induced reproductive toxicity, prostate cancer and Zn effects. The expressions of Metallothionein (MT) genes, proto-oncogenes, i.e., c-jun and c-fos genes and tumor-suppressor gene p53 in prostate and testes of rats were detected by RT-PCR and changes of testosterone level in serum were measured by radioimmunoassay after administration of Cd and Zn to rats.

In the present study, 1 mmol/kg Zn markedly prevented degenerative testicular lesion and reduced the effects of Cd (20 μmol/kg, i.m) in rats, even though the study showed that 1 mmol/kg Zn significantly decreased the circulating testosterone levels.

It is known that overexpressions of pro-oncogenes and decreased expression of tumor-supressor genes play a role in the occurrence of tumors. In this study, high dose Cd (20 μmol/kg s.c or i.m) induced c-jun gene expression in prostate and c-fos gene expression in VP or/and testes. Furthermore, i.m injection of Cd induced more pronounced changes in the expression of the above genes in VP than s.c injection did.

In the present study, low or high dose Cd (5 or 20 μmol/kg s.c.) enhanced MT-I gene expression in VP and low dose Cd induced MT-II gene expression in testes, while MT-III gene expression was slightly reduced by Cd (s.c). Injection i.m with Cd did not significantly increase MT-I gene expression in VP and testes, but MT-II and -III gene expressions decreased when detectable. It indicated that i.m. injection with Cd led to low levels of MT-I, II and III gene expression in VP compared with s.c injection, which could be one of the reasons why Cd (i.m.) injection (according to the findings of Waalkes *et al.* 1999) causes higher incidence of prostatic tumor in VP than s.c. injection.

Zn is effective in reducing the toxicity and/or carcinogenicity of Cd, but the exact mechanism is unknown. This study showed that Zn supressed c-jun gene expression in VP, while increased MT-I gene expression in DP and VP, stimulated MT-II gene expression in testes, induced MT-III gene expression in VP, and enhanced p53 gene expression in testes of rats induced by high dose Cd. It seemed that the protective effect of Zn on prostate cancer could be associated with its direct or indirect mechanism, that is, Zn could directly decrease c-jun gene expression in VP and enhance induction of MT-I and MT-III gene expressions, thus decreasing the incidence of cancer in VP, which is the main target site of prostatic tumor induced by Cd, or increased MT-II and p53 gene expressions in testes which could maintain its function and secretion of testosterone.

In summary, this study showed that the Cd-induced toxicity and events leading to cancer in testis and prostate is a complex process. The reduced testosterone production could not give an exact explanation for the initiation of prostate cancer, because Cd and Zn both decreased the level of testosterone, but there are different effects on prostatic tumor. Abnomal expression of proto-oncogenes and tumor-suppressor genes might

be associated with Cd carcinogenesis in prostate and testes. The most interesting findings were that high dose Cd (i.m.), increased c-jun and c-fos gene expressions and decreased p53, MT-I, II, and III gene expressions in VP of rats, which could be the reason that prostate tumor induced by Cd is mostly detected in VP of rats. Similar results have previously been reported by Xu *et al.* (1999) and Zhou *et al.* (1999). The modulation of Zn on toxicity or carcinogenesis of Cd in prostate and testes could be related to the following mechanisms: (1) Directly decreased c-jun gene expression and enhanced MT-I and MT-III gene expressions in VP. (2) Induced MT-II and p53 gene expression in testes and maintained its function and scretion of testosterone, which indirectly protected from carcinogenesis of Cd. Those findings could form a basis for considering the above molecules related to reproductive toxicity and prostatic tumor induced by Cd, as potential biomarkers of human prostate cancer in future research.

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