Mechanism of Cadmium-induced Testicular Cancer in Rats

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Introduction
Administration of Cd by the parenteral route induces testicular cancer in high incidence, although the underlying mechanisms for initiation of this carcinogenic process are only partially understood. Considering that early occurrence of ischemic damage to the testis is a prominent pathological feature following administration of carcinogenic dose of Cd, it is hypothesized that active oxygen species play a pivotal role in the initiation of the carcinogenic process by the metal. The purpose of the present study was to clarify the mechanism by which Cd initiates the carcinogenic process in rat testis in relation to oxidative stress generated in the tissue after a carcinogenic dose of Cd.

Methods
Male Wistar strain rats weighing 170–300g were used in this study. Rats were randomly divided into three groups: Group 1 served as the control; Group 2 received a single s.c. injection of a noncarcinogenic dose, 4.0 μmol/kg body weight, of CdCl2·2H2O; and Group 3 was treated s.c. with a single carcinogenic dose, 30 μmol/kg body weight, of the metal. Leydig cells were isolated by the collagenase dispersion method. Fe contents were determined by atomic absorption spectrophotometry and the o-phenanthroline method, respectively. Lipid peroxidation levels were estimated by the thiobarbituric acid method. Glutathione peroxidase, glutathione reductase, catalase, superoxide dismutase and xanthine oxidase activities were assayed using 1000 × g and 40000 × g supernatants of cell homogenates, respectively. Cellular production of H2O2 in Leydig cells was estimated by dichlorofluorescein method and glutathione levels were analyzed by the o-

phthalaldehyde method.

Results
A carcinogenic dose of Cd caused severe hemorrhagic damage in the testis within the first 12 h after the metal treatment. Twelve hours later, lipid peroxidation levels, Fe content and cellular production of H2O2 in Leydig cells were elevated, glutathione peroxidase activity had risen and glutathione reductase and catalase activities were reduced. Xanthine oxidase in Leydig cells also rose 6 and 9 h after the Cd treatment. Reduced glutathione content in testis and Leydig cells decreased 12 h after exposure to the carcinogenic dose.

Discussion
The results in the present study indicate that within 12 h a carcinogenic dose of Cd induced oxidative damage in the testicular tissue including Leydig cells, a target cell population for Cd carcinogenesis, as reflected by higher lipid peroxidation levels and decreased concentration of reduced glutathione. Thus, active oxygen species play a major role in initiation of the carcinogenic process. Enhanced production of H2O2 and the rise in xanthine oxidase activity in Leydig cells after the Cd treatment suggest that the mitochondria are a major intracellular source for generation of active oxygen species. On the other hand, decline in glutathione reductase and catalase activities suggests that the carcinogenic dose of Cd compromise cellular defense mechanism against oxidative stress.

In summary, the present study suggests that active oxygen species such as H2O2, caused by a carcinogenic dose of Cd may play a major role in the initiation of Leydig cells.