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Nickel-Induced Oxidative Stress in Testis of Mice: Evidence of DNA Damage and Genotoxic Effects

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Oxidative stress (OS) mechanisms are speculated to play a significant role in nickel-induced toxic effects and their carcinogenic potency. Although nickel-induced oxidative damage in somatic tissues is well demonstrated, evidence of the involvement of a similar mechanism(s) in nickel-induced testicular dysfunction and associated genotoxic effects is scarce. Hence, the present study aimed to investigate the nickel-induced OS response in testis and the associated genotoxic implications in vivo. Initially, the toxicity profile of nickel chloride was determined in adult albino mice (CFT-Swiss) following administration (intraperitoneal) of single doses. Subsequently, multiple sublethal doses (1.25, 2.5, and 5.0 µmol/100 g of body weight per day for 3 days) were used to characterize effects on testicular histoarchitecture, lipid peroxidation (LPO) in testis (homogenates, microsomal or mitochondrial fractions) and epididymal sperm, DNA damage, induction of apoptosis in testis, and incidence of sperm head abnormalities. Although short-term doses of nickel induced only a minimal LPO response, multiple doses elicited a moderate (15% to 30%) increase in LPO in whole homogenates and higher dose-related increases in both mitochondrial (20% to 50%) and microsomal fractions (25% to 60%). This was associated with a significant increase in DNA damage in the testis as evidenced by increased single-strand breaks (fluorimetric analysis of DNA unwinding assay). Further, at higher doses, nickel-induced apoptosis was demonstrable in the testis biochemically. Although caudal sperm counts determined at all sampling weeks showed no alterations, analysis for head abnormalities revealed a nearly 3- to 4-fold increase in the percentage of abnormal sperms among the nickel-treated males during the first 3 weeks. Furthermore, mating of nickel-treated (2.5 µmol/100 g of body weight per day for 5 days) males sequentially for a period of 5 weeks with untreated females resulted in a significant increase in male-mediated dominant lethal–type mutations (the frequency of dead implantations) during the first 3 weeks, suggesting a stage-specific effect on postmeiotic germ cells. These findings suggest that testicular toxicity of nickel compounds may be related to enhanced production of reactive oxygen species, probably mediated through oxidative damage to macromolecules, including damage to DNA.

Key words: Nickel chloride, oxidative damage, apoptosis, abnormal sperms, dominant lethal mutations

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