Study of Effects Induced by Chronic Low Dose Ingestion of Uranium on Testicular Steroidogenesis in Rat

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Uranium, a heavy metal and natural radionuclide, presents both radiotoxicant and chemotoxicant properties. Uranium present in ground can be spread out in environment by mining, but can also be found in drinking water of areas where high concentrations are present in soil. Besides its natural presence, uranium contamination of water or food chain can occurs through nuclear industry or military army. Natural uranium can be chemically enriched (increasing its radiological activity). The by-product of the process, called depleted uranium present a lower radiological activity. Few studies on biological effects of chronic contamination with low doses of uranium have been conducted, especially on endocrine system and steroid hormones. Nevertheless, an epidemiologic study of Namibian uranium miners reveals a decrease in their testosterone circulating level. Steroid hormones are synthesized from cholesterol mainly by gonads and adrenals. The two main testicular steroid hormones are testosterone and estradiol. These hormones regulate the development and persistence of testis functions, necessary for reproduction. Three enzyme families are involved in steroid hormone synthesis: cytochrome P450 (CYP), hydroxy-steroid dehydrogenase and 5alpha-reductase enzymes. They are mainly transcriptionaly regulated via nuclear receptors and transcription factors. To mimic potential public contamination with water or food chain, we develop a rodent model of contamination with non-nephrotoxic dose of uranium through drinking water (40mg/L). Adult males' rats were contaminated during nine months (equivalent to twenty years for human) with depleted or enriched uranium, to distinguish chemical versus radiological effects. Depleted and enriched uranium did not affect animals' general health status (food and water intake, weight gain). Moreover, the lack of nephrotoxicity was confirmed by normal creatinine and urea levels, as well as histological kidney analysis. Depleted uranium did not seem to significantly affect production of testicular steroid hormones in rats. In the same way, it does not affect expression of genes involved in their biosynthesis pathway. Inversely, enriched uranium significantly increased the level of circulating testosterone (by 2.5 fold), pointed out significant increases in the mRNA levels of synthesis enzymes (e.g. cyp11a1 2.2 fold, cyp19a1 2.3 fold) and transcription factors such as SF-1 (64%) or GATA-4 (87%). In conclusion, our results show for the first time a differential effect among depleted or enriched uranium contamination on the testicular steroidogenesis. Indeed, depleted uranium does not seem to affect this metabolism, while enriched uranium does. Thus, it seems that in our experimental conditions, testicular steroidogenesis is more sensitive to radiological than chemical properties of uranium.

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