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Combined action of uranium and stress in the rat II. Effects on male reproduction

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Abstract

The effects of stress on the potential reproductive toxicity of long-term exposure to uranyl acetate dihydrate (UAD) were assessed in adult male rats. Six groups of animals were given UAD at 10, 20, and 40 mg/kg/day in the drinking water during 3 months. Animals in three of these groups were also subjected to restraint for 2 h/day during the same period. Control groups included restrained and unrestrained male rats not exposed to UAD. To evaluate the fertility, male rats were mated with untreated females for 2 weeks. Although body weight was not affected by uranium at any dose, there was a significant (not dose-related) decrease in the pregnancy rate. Moreover, spermatid number/testis was significantly decreased by uranium administration. Histopathological examination of the testes in rats killed after 3 months of treatment revealed few differences in the tubule and interstitial alterations (focal atrophy, binucleated cells) between control and uranium-exposed animals. The results of this investigation show that at the current UAD doses, restraint stress did not enhance the uranium-induced adverse effects on reproduction in male rats.

Keywords: Rats; Uranyl acetate dihydrate; Restraint stress; Reproductive toxicology; Uranium concentrations

1. Introduction

Uranium exposure can result in both chemical and radiological toxicity. However, in general, chemical toxic effects from uranium compounds occur at lower exposure levels than radiological toxicity (Domingo, 1995; Hartmann et al., 2000). There is an extensive literature on the general toxicity of uranium (U) from inhalation, ingestion, and injection exposures (Taylor and Taylor, 1997; ATSDR, 1999; WHO, 2001; Sheppard et al., 2005). However, until recent years little attention was paid to the potential toxic effects on ura-

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nium on reproduction and development (Corbella and Domingo, 1996; Arfsten et al., 2001; Domingo, 2001; Craft et al., 2004). In addition, most experimental studies on uranium-induced reproductive and developmental toxicity have been performed in a sole species of mammals, mice (Domingo et al., 1989a, 1989b; Paternain et al., 1989; Llobet et al., 1991; Bosque et al., 1994).

In recent years, the environmental concentrations of uranium have increased in some regions as a consequence of the military use of depleted uranium (DU) weapons by NATO and other military organizations. The use of DU ammunition and possible links between the exposure of military personnel to DU fine particles and the Gulf War Syndrome has generated a great interest on the medical and environmental fate of DU (McDiarmid, 2001; McDiarmid et al., 2000, 2004; Abu-Qare and Abou-Donia, 2002). Moreover, uranium contamination becomes dispersed across the natural environment, thus entering the food chain. It means that for certain populations, the chemical toxic effects on reproduction and development of uranium intake can be a matter of notable concern (Domingo, 2001; Arruda-Neto et al., 2004).

On the other hand, it is important to remark that the military personnel exposed to uranium, as well as the subjects living in uranium strike areas have been also probably subjected to remarkable stressful events or experiences. Stress is a highly individualized response of an organism to external or internal challenges that the individual cannot control or can control only with difficulty (Vogel, 1993). In recent years, a number of experimental studies in mammals have demonstrated that during pregnancy, maternal stress may enhance the metal-induced adverse effects on embryo/fetal and postnatal development (Domingo et al., 2004). In relation to uranium, in recent decades it has been demonstrated that this metal is a maternal, and developmental toxicant when given orally at relatively low doses to rats and mice (Domingo et al., 1989a, 1989b; Paternain et al., 1989; Albina et al., 2003). Moreover, in a study performed in our laboratory, in which untreated females were mated with male Swiss mice that received UAD in the drinking water for 64 days at 0, 10, 20, 40, and 80 mg/kg/day, a significant decrease in the pregnancy rate was observed (Llobet et al., 1991), while body weights were significantly reduced at 80 mg/kg/day. Testicular function/spermatogenesis was not affected by uranium at any dose, as evidenced by normal testes and epididymis weights and normal spermatogenesis. Histopathological examination of the testes did not reveal any significant difference between controls and uranium-exposed animals, with the exception of an increase in Leydig cells vacuolization at 80 mg/kg/day. However, in a previous study in which mature male mice were given by gavage 0 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, or 25 mg/kg/day UAD for 60 days prior to mating with mature virgin female mice exposed to the same uranium doses for 14 days prior to mating, no adverse effects of uranium on fertility were evident at any dose, while embryolethality was observed at 25 mg/kg/day (Paternain et al., 1989).

Taking into account that humans be potentially exposed to uranium through the diet, inhalation, or can experience contamination through wounds (ATSDR, 1999; WHO, 2001), while they can be also concurrently subjected to stressful situations, the main objective of the present study was to assess whether stress could enhance the potential adverse effects of uranium on reproduction in adult male rats. Restraint was used as the experimental model of stress. It is an easily controlled stressor that imposes both physical and psychological demands on the subject (Paré and Glavin, 1986; Domingo et al., 2004).

2. Materials and methods

2.1. Chemical

Uranium was administered as uranyl acetate dihydrate (UAD), which was purchased from E. Merck (Darmstadt, Germany). UAD was dissolved in tap water and given at doses of 10, 20, and 40 mg/kg/day. These doses are approximately equal to 1/20, 1/10, and 1/5 of the acute oral LD_{50} of UAD in adult rats (Domingo et al., 1987).

2.2. Animals and treatment

Sexually mature male and female Sprague–Dawley rats (220–240 g) were obtained from Criffa (Barcelona, Spain). Animals were housed in plastic cages in a climate-controlled facility with a constant day–night cycle (light: 08:00–20:00 h) at a temperature of $22 \pm 2\,^{\circ}C$, and a relative humidity of $50 \pm 10\%$. After