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Mechanism of diethylhexylphthalate (DEHP) induced testicular damage and of grape seed extract-induced protection in the rat

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ABSTRACT

The aim of this study was to determine the effect of diethylhexylphthalate (DEHP) on testicular mitochondrial viability and lipid peroxidation as a possible novel mechanism of PEHP testicular toxicity and whether grape seed extract (GSE) beneficially influences the mitochondrial function in testes of rats exposed to diethylhexylphthalate (DEHP). Sixty male albino rats were divided into three groups (n = 20): group I: was used as a control, group II: received diethylhexylphthalate (DEHP) (500 mg/kg/day orally) alone for 30 days, and group III: received the same DEHP dose in combination with GSE (proanthocyanidins) (100 mg/kg body weight). DEHP administration significantly decreases the testicular mitochondrial viability, mRNA expression of androgen receptors (AR), testosterone hormone concentration, increases mRNA expression of INOS and as compared to control group. It also decreases reduced glutathione (GSH) concentration, glutathione reductase (GR), super oxide dismutase (SOD), Catalase activities and increases lipid peroxidation (LPO) and DNA fragmentation%. In synchronization, a substantial decrease of testicular & epididymal weight and volume which accompanied by considerable alteration of semen character. Grape seed extract (GSE) alleviates the toxic effects of DEHP by increasing the mitochondrial viability, decreases the lipid peroxidation, and increases the testicular antioxidant activity. Our results were confirmed by histopathological and immunhistochemical studies.

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1. Introduction

Endocrine disruptors include a large group of environmental pollutants that behave as agonists or antagonists of androgens and estrogens and that have long been suspected of being involved in the occurrence of male reproductive defects observed in humans, including cryptorchidism, hypospadias, testicular cancer and poor semen quality. In industrialized societies, humans are exposed to a wide spectrum of endocrine disruptors. Besides occupational exposure scenarios, exposures can also occur through air, dust, water, food and using consumer and personal-care products. From all these sources, chemicals end up in the human body primarily via ingestion, inhalation or dermal absorption (Culty et al., 2009; Koch and Calafat, 2009).

Among these compounds, the phthalic acid esters, or phthalates, used as plasticizers to impart flexibility in vinyl plastics and as fixatives and stabilizers in such disparate products as cosmetics, adhesives and lubricants. Phthalate esters can leach out overtime from these products leading to widespread, low level human exposure (Gaido et al., 2007).

Phthalates are widely used as general-purpose plasticizers in polymers, primarily in polyvinyl chloride (PVC) resins. Typical products containing phthalates are floorings, roofings, wall coverings and cables, clothing, packaging materials and toys. Di-2-ethylhexyl phthalate (DEHP) is the major plasticizer for PVC-containing medical devices such as bags for blood or parenteral nutrition, tubings and catheters. Because phthalates are not chemically bound to the polymer, they can leach or outgas into the surrounding media. Thus, phthalates can enter the environmental cycles or the human body directly. Phthalates also are used as industrial solvents and lubricants, additives in the textile industry, in pesticide formulations and as components in personal-care products. One of them, dibutyl phthalate (DBP), is also used in the pharmaceutical field as a constituent of the enteric coating of some medications (Koch and Calafat, 2009).

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Evidence of widespread human exposure to phthalates and toxicological studies showing that some phthalates are developmental and reproductive toxicants in animals has raised both scientific and public concern about the ubiquitous use of phthalates in consumer and personal care products. Phthalates are industrial chemicals with many uses, including making polyvinylchloride plastics flexible and holding color and scent in personal care products. Phthalates can be found in perfumes and cologne, paints, insect repellent, medication coatings, hairspray, shampoo and medical devices including i.v. bags, infusion tubing, and dialysis bags. As a result of their ubiquitous use, phthalates are present in food, air and water (Duty et al., 2005).

DEHP is found in amniotic fluid, placenta and fetal tissues of rats following ingestion, suggesting that DEHP might have an effect on the development of embryonic tissues. Although the typical human exposure to DEHP ranges from 3 to 30 μg/kg/day, specific medical conditions exist in which DEHP exposure can reach much higher levels, from 1.5 mg/kg/day during hemodialysis to between 10 and 20 mg/kg/day through neonatal transfusion or parenteral nutrition (Culty et al., 2008).

Since DEHP is lipophilic and not chemically bound to PVC, it can leach out of PVC medical devices. The amount of DEHP leaching depends on the lipophilicity of the fluid in contact with the devices. Thus, substances, such as blood, i.v. lipid emulsion, or total parenteral nutrition (TPN) solution, and surfactants used to solubilize i.v. medications can readily extract DEHP from PVC tubing and containers. Anticancer drugs, such as paclitaxel, docetaxel, teniposide, and etoposide are widely used for various chemotherapies, and contain such surfactant as either polysorbate80 or polyoxyethylated castor oil. Exposure to DEHP has produced adverse effects in laboratory animals. However, no studies have been performed to evaluate the effects of DEHP exposure in humans. In particular, cancer patients may receive multiple interventions, including cancer chemotherapy, TPN, and blood transfusion, whose treatment may have potential risk of DEHP exposure (Takeshita et al., 2006).

Zhang et al. (2014) showed that exposure to DEHP at 150 mg/kg/bw induced a testicular damage and this was manifested by decrease of the thickness of seminiferous epithelium and decrease of the number of cell layers which was around 3–4 layers.

Chen et al. (2015) showed that lactating exposure to DEHP caused hyperplasia of the progenitor leydig cells with decreased number of spermatogenic cells in seminiferous tubules. Furthermore, Hirai et al. (2015) added that low dose exposure to DEHP caused functional damage to the blood testes barrier with an increase in testicular number of interferon gamma positive cells and resulted in the production of autoantibodies targeting haploid cells.

The main function of the testis is the production of spermatozoa in the process of spermatogenesis which is precisely regulated by androgens (Carreau and Hess, 2010).

Animal testing of phthalates has been conducted at doses far higher than those present in the ambient human environment. In addition, until recently phthalates were tested singly, while humans are exposed to multiple phthalates simultaneously. Recent rodent data suggest that exposure to multiple phthalates at low doses conveys risk in a dose additive manner. This suggests that the risk from a mixture of phthalates (or phthalates and other antiandrogens), whether acting by similar mechanisms or not, cannot be accurately assessed studying one chemical at a time. The same may be true of risks from multiple exposure routes. For example, most toxicological testing of phthalate is via oral exposure. However, humans are exposed to phthalates by a multiplicity of routes. For DEP, and its metabolite MEP, human exposure is predominantly dermal. Whether differences in exposure route can account for differences in the toxicology of this phthalate in humans and rodents is not clear (Swan, 2008).

Because of these important differences in route, dose level and multiplicity of agents, we used a high dose of DEHP.

Little is known about the chronic toxicity of diethyl phthalate. Some studies suggest that phthalates affect male reproductive development via inhibition of androgen biosynthesis. In rats, for instance, repeated administration of DEP results in loss of germ cell populations in the testis. However, diethyl phthalate doesn't alter sexual differentiation in male rats (Foster et al., 1981).

The mode of action of the toxic effects of phthalates to the male reproductive system has not yet been satisfactorily explained. An impairment of testosterone metabolism in testes of adolescent male rats has been observed, which is probably due to a number of factors. Kim et al. (2004) reported that testicular impairment and tubular atrophy were especially aggravated by hormone regulation disturbances that cause a decrease in the production of testosterone in testes, by adverse effects of reactive oxygen species and by testicular cell apoptosis. The impairment of the male reproductive system due to the DEHP is also caused by alterations of the cytosolic phospholipase enzyme A2 (cPLA2) and of enzymes that metabolise the arachidonic acid. Shirota et al. (2005) has been reported that DEHP has a direct toxic effect on the testicular structure and spermatogenesis at a dose of 250 and 500 mg/kg/day but at a dose of 125 mg/kg has no observed effect on testicular development in rats.

Androgens exert their cellular effects via androgen receptors (ARs) of the nuclear receptor superfamily and act as ligand-dependent transcription factors (Lee et al., 2012). After the binding of androgens, ARs undergo a conformational change, dimerization, translocation to the cell nucleus and binding to specific DNA sequence, thus modulating expression of target genes (Yong et al., 2003). There is a general agreement that ARs can be detected within the seminiferous epithelium in nuclei of Sertoli cells, peritubular myoid cells, interstitial Leydig cells and perivascular smooth muscle cells (Wang et al., 2009).

Grape seed extract is a rich source of one of the most beneficial group of plant flavonoids. Grape seed extract (GSE) contains a number of polyphenols, including procyanidins and proanthocyanidins, which are powerful free radical scavengers.

Grape seed proanthocyanidin extract is a rich source of polyphenolic antioxidants, a naturally occurring family of oligomeric proanthocyanidins found in a wide range of fruit and vegetables (Bagchi et al., 2000). A number of studies have demonstrated the superior free radical scavenging ability of GSE as compared to vitamins C, E and β-carotene (Rapport and Lockwood, 2001). These flavonoids exert many health effects. Such as increasing intracellular vitamin C level, increasing the capillary permeability and scavenge antioxidants and free radicals (Ozer et al., 2011).

This study was conducted to investigate mechanism of the toxic effect of DEHP on the testis of adult male albino rats and to determine the possible protective effect of GSE on these changes.

2. Materials and methods

2.1. Chemicals

All chemicals were purchased from Sigma–Aldrich Corporation (St. Louis, MO).

2.2. Animals

In this study, 60 male albino rats of average weight (150–200 g) were used. The animals were housed at the animal house, Faculty of Medicine and were kept under conditions of adequate ventilation and temperature, received a standard pallet diet and were allowed

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