Vision: Journal of Biomedical Research & Environmental Sciences main aim is to enhance the importance of science and technology to the scientific community and also to provide an equal opportunity to seek and share ideas to all our researchers and scientists without any barriers to develop their career and helping in their development of discovering the world.
SHORT COMMUNICATION

Diethylhexylphthalate–A Worthful to Pay Attention Risk Factor for Benign Prostate Hyperplasia

Aibo Pang, Cunbao Ling, Wei Huang, Yangyang Wu, Chunyan Zhang and Yaping Tian*

Birth Defects Prevention and Control Technology Research Center, Chinese PLA General Hospital, Beijing, 100853, China

*Corresponding author(s)
Yaping Tian, Birth Defects Prevention and Control Technology Research Center, Chinese PLA General Hospital, Beijing, China
ORCID: 0000-0002-8245-3745
E-mail: tianyp@301hospital.com.cn
DOI: 10.37871/jbres1592
Submitted: 26 October 2022
Accepted: 29 October 2022
Published: 31 October 2022
Copyright: © 2022 Pang A, et al. Distributed under Creative Commons CC-BY 4.0

ABSTRACT

The metabolism of plasticizing phthalates may correlate with an increased risk of benign prostatic hyperplasia in humans. Diethylphthalate (DEHP) and its metabolites interfere with sex hormone function, causing inflammation and oxidative stress at low doses. The effects may contribute to the development of benign prostate hyperplasia.

Introduction

Diethylhexylphthalate (DEHP), an environmental endocrine disruptor, is widely used in daily goods, medical devices and other paraphernalia such as IV bags, tubing, etc. Its long-term chronic risks could not be ignored. To date, there is insufficient current evidence to prove a causal relationship between DEHP and BPH. The effect of DEHP and its metabolism in vivo on the development of BPH have been discussed in this manuscript and it would be benefit on the better understanding and prevention of BPH.

DEHP metabolism

The metabolic mechanisms of DEHP in organisms can elucidate important findings with clinical implications for its biomonitoring. The half-life of DEHP in humans and rodents is less than 24h [1–4]. Pharmacokinetic studies in rat models reveal that the toxicity of DEHP may depend on its biotransformation to related metabolites in vivo [5]. In humans, DEHP is absorbed in the intestines of humans and hydrolyzed to monoester phthalate (MEHP), as well as other hydroxylated or oxidized products. MEHP is significantly more toxic, approximately 10 times more potent than DEHP, and has been mentioned in previous pathogenicity studies [6]. DEHP is eventually excreted in the urine. Urine samples are better than blood samples when testing for DEHP intermediates, such as MEHP, oxidized metabolite monoester phthalate, mono (2-ethyl-5-hydroxyhexyl)-phthalate, and mono (5-carboxy-2-ethylpentyl) phthalate. These metabolites are effective biomarkers for studying the severity of human exposure to DEHP because of the low matrix interference and high levels of sensitivity during the detection process. Generally, for testing, the urine samples are extracted with a suitable solvent. The extract is purified and filtered as needed, concentrated, and analyzed using gas chromatography–mass spectrometry (GC–MS). By method optimization, more DEHP intermediates and transformation products can be further analyzed comprehensively which will be helpful in fully understanding their metabolisms and biological significance.

The relationship between DEHP exposure and BPH

DEHP and its metabolites interfere with sex hormone levels in the body [7–9]. Prostate growth, development, and proliferation are regulated through the synergistic effects of estrogen and androgens. Since prostate cells tend to proliferate with age, hormonal imbalances in the body may lead to accelerated prostate hyperplasia. Most of the current studies are based on in vitro and in vivo animal tests that are mostly focused on reproductive function and prostate weight. A BPH diagnosis in the clinic mainly relies on histopathological criteria, and changes in prostate weight are not equal to pathological changes. DEHP has estrogen-like effects and competes with endogenous estrogens for plasma sex hormone binding proteins [10], slows their inactivation, and upregulates the number of Estrogen Receptors (ER), which increases target organs’ responsiveness to estrogen, which in turn leads to increased bioavailability of endogenous estrogens. In addition, DEPH has the following biological effects: (1) prevents adenosine-3’, 5’-cyclic monophosphate inactivation by inhibiting the expression of luteinizing hormone receptors and levels of acute regulatory proteins of steroid hormone synthesis in testicular mesenchymal cells [11]; (2) affects testosterone synthesis by inducing estrogen formation from androgens in the presence of aromatase and inhibiting the activities of 3βHSD, cytochrome P450, and 17βHSD [12]; and (3) inducing testicular mesenchymal cell apoptosis through PI3K/AKT/mTOR signaling [13]. In other words, DEHP interferes with the synthesis, metabolism, and utilization of endogenous environmental hormones through multiple pathways, and ultimately mediates the abnormal proliferation of prostate stromal cells by targeting reproductive organs [14]. DEHP could potentially stimulate cell proliferation by upregulating Androgen Receptor (AR) expression and interfering with gene pathways, such as the P38 pathway. Uregulation of EGF/EGFR increases the sensitivity of the prostate to androgen stimulation. Data from the 2001–2008 National Health and Nutrition Examination Survey (NHANES) investigates a potential between DEHP and BPH, which is biphasic and concentration-dependent [15]. The principle underlying the effect of DEHP on BPH may be similar to the inverted U-shaped relationship that exists between estrogen concentration and prostate stromal cell proliferation, which is a nonlinear relationship.

A study that followed 10,000 Americans for eight years found that higher levels of DEHP are associated with higher levels of inflammation and oxidative stress [16]. DEHP metabolites that enter the body can disrupt mitochondrial function and produce excess Reactive Oxidants (ROS), reducing the activity of antioxidant enzymes, superoxide dismutase, catalase, and glutathione transferase. Oxidative stress damages cellular DNA and mediates cellular damage and inflammation. In addition, DEHP affects fat and carbohydrate metabolism and alters the intestinal flora [17]. MEHP activates peroxisome proliferator-activated receptors, promotes preadipocyte differentiation, and affects glucose uptake and triacylglycerol deposition, which may increase the risk of metabolic diseases and promote obesity [18]. International studies have confirmed that BPH development is associated with metabolic syndrome. Although DEHP is not immunogenic, it acts as an immune adjuvant that enhances immune antigen activity, promotes IL-4 gene expression, generates a helper T cell2 (Th2)-type immune responses, and leads to Th1/Th2 imbalances. DEHP also activates nuclear factors in activated T cells, which enter the nucleus from the stroma. A survey suggests macrophages secret inflammatory and chemokines after phagocytosing DEHP. These inflammatory factors mainly include Interleukin-8 (IL–8), C–X–Cmotif ligands (CXCL1), CXCL2, CXCL3, CXCL6, Matrix Metalliproteinase10, Colony-stimulating factor–2, Tumor necrosis factor–α,IL–1, and IL–6, which exacerbates inflammatory and allergic responses [19]. These chemokines are also correlated with the progression of early prostatitis and BPH.

Future Research

Evidence on the relationship between DEHP and BPH is inconsistent due to limited research. Most animal experiments have shown that experimental DEHP exposure doses are greater than the daily exposure of humans. The dose stratification of DEHP has not been defined in humans. The effects of DEHP on prostate cell proliferation are related to the duration and intensity of the exposure. DEHP-mediated damage to organisms involves multiple factors and pathways, which mainly leads to sex hormone disorders. The specific mechanisms underlying the effects of DEHP on humans need to be studied systematically, using large cohorts and sensitive populations to elucidate its pathogenesis and determine novel prevention and control methods. In addition, DEHP exposure also varies depending on the diet and lifestyle of the observed population in a different region. Thus, multicenter, cross-regional, and multidisciplinary joint studies will help obtain more accurate data on DEHP pathogenesis, risk assessment, and prevention and control strategies.

Acknowledgment

We would like to thank Edit age (www.editage.cn) for English language editing.

Key Project “Proactive health and aging technology responses” of National Key Research and Development Project of China (2021Yfc2009300).

References


3. Milman HA, Bosland MC, Walden PD, Heinze JE. Evaluation of the adequacy of


