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YOUNG INVESTIGATOR REVIEW

Endocrine-disrupting chemicals and male reproductive health

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Abstract Endocrine-disrupting chemicals are substances present in the environment that can interfere with normal hormonal balance and thus exert potentially adverse health effects on the human organism. Male reproductive system development and function may be susceptible to the effects of such environmental toxicants. Bisphenol A, phthalates and alkylphenols are important components of multiple products and are thus ubiquitously present in the environment. It has been demonstrated under laboratory conditions that they can exert detrimental effects on the male reproductive system. However, human exposure data are scarce and do not uniformly support toxicity of these substances at environmental concentrations. Despite substantial research efforts, the final answer to the problem of endocrine-disrupting chemicals is not yet in sight.

KEYWORDS: alkylphenols, bisphenol A, endocrine-disrupting chemicals, male reproductive health, phthalates

Introduction

Endocrine-disrupting chemicals are a heterogeneous group of substances that began to attract attention two decades ago due to possible harmful effects (Colborn et al., 1993). According to the US Environmental Protection Agency, an endocrine-disrupting chemical is defined as 'an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes' (Kavlock et al., 1996). Considering reproductive function, most of the effects are exerted through disturbance of oestrogen- or androgen-mediated processes. In many reports written in the last two decades, increasing exposure to these substances has even been proposed as the mechanism for decreasing male reproductive function and lower average sperm counts, although the hypotheses about deteriorating male reproductive capabilities are controversial (Andersson et al., 2008; Carlsen et al., 1992; Jouannet et al., 2001; Safe, 2012). The use of some of the established toxic substances, such as polychlorinated biphenyls or

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polybrominated diphenyl ethers, has been restricted or even banned in the Western world. Nonetheless, many of these substances can still be detected in considerable concentrations in the environment (Rudel and Perovich, 2009). Moreover, unresolved controversies around certain other compounds, including bisphenol A and phthalates, have resulted in increasing exposure to these chemicals in the last decades.

This brief review will critically investigate the possible effects of bisphenol A, phthalates and alkylphenols on the male reproductive system and current research efforts. First, the production, use and sources of exposure to discussed endocrine-disrupting chemicals will be presented. Second, possible mechanisms of action and demonstrated effects in laboratory conditions will be discussed. Finally, the current evidence of possible effects of bisphenol A, phthalates and alkylphenols on the human male reproductive system is reviewed.

Production and human exposure

Bisphenol A, phthalates and alkylphenols are important components of many industrial processes. Although exact quantities are difficult to estimate, it is reckoned that around 6 million tonnes of phthalates are produced worldwide every year (Rudel and Perovich, 2009). For bisphenol A, estimates range 2.2—4.7 million tonnes, of which around 1.2 million tonnes are produced in the EU, and the amounts are rising by about 6—8% yearly (Fernandez, 2010; Huang et al., 2012). The annual production of alkylphenols has been estimated to be 154,000 tonnes in the USA and 75,000 tonnes in the EU (Soares et al., 2008). Since these data were published, the use of alkylphenols has been restricted in the EU, but they are still found in considerable concentrations in the environment (Soares et al., 2008). All of these substances or their metabolites have been detected in human urine, serum, amniotic fluid of pregnant women, in breast milk and even in semen (Calafat et al., 2005; Guenther et al., 2002; Huang et al., 2009; Main et al., 2006).

Bisphenol A is one of the most investigated and, for many authors, one of the most potent endocrine-disrupting chemicals (Maffini et al., 2006). It is extensively used in polycarbonate plastic and epoxy resin production. Thus, bisphenol A can be found in plastic water bottles, food containers, a variety of household products (e.g. compact disks, consumer electronics), medical equipment (e.g. dental fillings) and thermal paper. Human exposure is widespread, as every large biomonitoring study has detected bisphenol A in more than 90% of tested samples (Vandenberg et al., 2010). The largest yet-performed study, the US National Health and Nutrition Examination Survey detected bisphenol A in the urine samples of 92.6% of US males (Calafat et al., 2008). Current knowledge suggests that the oral route is most important for bisphenol A exposure (Geens et al., 2012). However, several authors suggest that alternative routes, such as inhalation or transdermal absorption, may be underestimated sources of exposure (Stahlhut et al., 2009).

Diesters of 1,2-benzenedicarboxylic acid (phthalic acid), commonly referred to as phthalates, are a group of substances widely used in industry and thus ubiquitously present in many everyday products. High-molecular-weight phthalates (e.g. di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate and di(*n*-octyl) phthalate) are mainly used as plasticizers in the manufacture of flexible vinyl, whilst low-molecular-weight phthalates (e.g. diethyl phthalate and dibutyl phthalate (DBP)) are used in personal care products. Thus, they can be found in food containers, vinyl upholstery, adhesives, perfumes and eye shadow. However, they are not covalently bound to plastic material and consequently can be released into the environment with time and the use of products. Like bisphenol A, their metabolites can be widely detected in the population. Thus metabolites of the parent compounds have been found in the vast majority of males in the USA (Silva et al., 2004). Similarly to bisphenol A, the exposure to phthalates is primarily through oral intake, although transdermal route or inhalation may contribute significantly (Rudel and Perovich, 2009).

Alkylphenol ethoxylates are a group of substances most commonly used as surfactants in common consumer products, such as detergents, disinfectants, surface cleaners, cosmetic products, spermicides and pesticides. The most important members of this group are nonylphenol ethoxylate and octylphenol ethoxylate (Tubau et al., 2010). These substances undergo metabolic breakdown in the environment and lose ethlylene oxide side chains to become alkylphenols (4-*n*-octylphenol and 4-*n*-nonylphenol). Unlike most of the exogenous chemicals, which usually become less toxic with biodegradation, alkylphenols actually increase their toxicity during this process. Alkylphenols are frequently found in wastewaters (White et al., 1994; Ying et al., 2002) and are also present in food (Guenther et al., 2002). Ingestion routes have not been definitely described, but primarily oral ingestion and secondarily inhalation and transdermal route are most likely (Wilson et al., 2001).

Mechanisms of action on the male reproductive system

A disturbance of the male reproductive system can take place at different periods of a lifetime. In order to study disturbances, it is important to consider first what is known of the physiological mechanisms that ultimately lead to healthy sperm production. The development of the male reproductive system requires the activation of specific pathways by hormones, notably androgens and anti-Müllerian hormone. Thus, although testis formation itself is not hormone dependent, most other aspects of masculinization depend on normal testicular hormone production. Furthermore, testis cell development (as opposed to testis formation) is dependent on the local action of hormones (Sharpe, 2001). Androgens are the most important hormones in the normal development of Wolffian ducts that differentiate into epididymis, vas deferens and seminal vesicles (Wilson, 1978). Dihydrotestosterone, which is produced locally from testosterone by 5-α-reductase, is the most important hormone in masculinization of external genitalia and prostate (Fisher, 2004). Hence, a balanced hormonal environment is essential for a normal development of the male genitourinary tract. Hormonal disturbances have been linked to masculinization anomalies, but little research has been performed to relate early hormone