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Endocrine disruption: Relevance of experimental studies in female animals to human studies

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Abstract

It has been hypothesized that in utero exposure to endocrine disruptors compounds (EDCs) plays a role in multiple diseases including breast cancer in women, obesity and related adverse health effects in females and males. The genesis of this hypothesis is from the Barker theory of the developmental origins of health and disease and also from the adverse health effects observed in the female and male offspring of mothers prescribed the potent estrogenic drug diethylstilbestrol (DES) during pregnancy. There is minimal evidence that in utero or later exposure to polychlorinated biphenyls (PCBs) or 1,1-bis(p-chlorophenyl)-2,2-dichloroethylene (DDE) correlates with an increased incidence of breast cancer and this is consistent with animal model studies. This review has also focused selectively on the hypothesized PCB/DDE-induced obesogenic effects in humans (primarily females and males combined) and in rodent models. In human epidemiological studies, most collective reports indicate that in utero exposure to PCBs does not increase BMIs whereas the results obtained for DDE are mixed; most relevant studies in animal models do not show any effects of these chemicals (in utero) on BMI values in offspring. It should also be noted that time-dependent diet/environmental-induced changes in microbiota also influence human diseases including obesity. Until this important contribution to human health and obesity is understood and corrected for, it may be premature to carry out extensive epidemiological studies on the effects of in utero exposure to EDCs on offspring.

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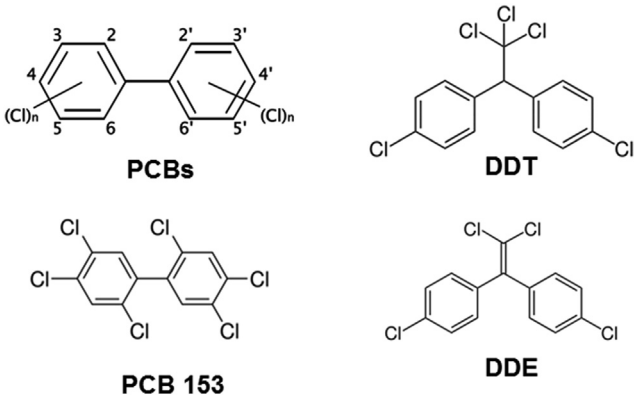
EDCs, Endocrine disruption, Organochlorines, Obesity.

1. Introduction

The potential adverse effects of endocrine disruptor compounds (EDCs) on human health were initially sparked by two studies on breast cancer in women and temporal changes in male sperm counts. Two small studies in Connecticut and New York reported higher levels of polychlorinated biphenyls (PCBs) or 1,1-bis(p-chlorophenyl)-2,2-dichloroethylene (DDE) respectively (Fig. 1) in breast cancer patients vs. controls [1,2]. It was subsequently hypothesized that "substances such as xenoestrogens increase the risk for breast cancer by mechanisms which include interactions with breast cancer susceptible genes" [3]. During the same time period, it was reported in a meta-analysis of sperm count studies from various clinics that sperm counts had decreased approximately 40% between 1938 and 1991 [4] and it was subsequently hypothesized by Sharpe and Skakkebaek that this may be due to in utero exposure to estrogenic compounds [5]. This hypothesis is consistent with the developmental origins of health and disease theory initially proposed by Barker [6]. The critical importance of in utero exposure for observing subsequent adverse effects in both male and female offspring was derived, in part, from the effects observed in both female and male offspring of women who had been administered the potent estrogenic compound diethylstilbestrol (DES) during pregnancy.

The endocrine disruptor hypothesis concerning the potential adverse effects of in utero exposures to EDCs has generated concerns of regulators and the public and has also resulted in ongoing controversies among scientists [7–13]. It was hypothesized that in utero exposures to EDCs may play a role in multiple diseases including obesity, diabetes, cardiovascular disease and neurologic deficits including attention deficit disorders [7–9,13]. The concerns regarding these compounds also include the potential impacts of EDC mixtures which may exacerbate the effects of these compounds [14]. However, it should also be noted that EDCs may interact antagonistically and exposure to trace contaminant levels of synthetic/environmental EDCs occurs in parallel with relatively high human exposure to endocrine-active phytochemicals and microbiota-derived compounds that tend to be health protective [15]. This opinion piece will focus on the relevance of experimental animal model studies as predictors of endocrine disruptor-mediated effects in humans with an emphasis on females (where possible). Selected case studies with respect to individual chemicals and specific human responses will be discussed and, in some of these studies, the EDC-induced effects on human responses such as obesity and diabetes are hypothesized responses. It should also be pointed out at the outset that

Figure 1



Structures of POPs: PCBs, PCB153, DDT and DDE.

a recent review indicated that laboratory animal models may not be good predictors of the endocrine-related obesity effects of organochlorine EDCs that have been hypothesized to occur in humans [16].

2. Endocrine disruptors: effects of in utero exposures on the offspring

2.1. Diethylstilbestrol

DES is a potent estrogenic drug that was administered in high doses (pharmacological) to pregnant women to maintain pregnancy and serious side effects were observed in DES-daughters and sons. One of the hallmarks of DES daughters is the increased incidence of vaginal clear cell adenocarcinoma [17] and multiple female reproductive tract abnormalities, infertility, poor pregnancy outcomes and early menopause [18,19]. In addition, there is evidence for up to two-fold increase in breast cancer in DES-exposed daughters [20–22] and evidence for a possible (but not consistent) increase in psychiatric disorders [23]. Thus, DES serves as an important model for predicting adverse effects resulting from in utero exposure to an estrogenic compound; however, it should be noted that the doses of DES administered to pregnant women were relatively high (2.5–150 mg/d in most studies) [24] and the estrogenic potency of DES is at least comparable to that of 17β-estradiol (E2) for most assays and responses. There are also claims that DES and other EDCs are obesogens [25,26] and EDC-induced obesogenicity is a major focus of EDC research. Hatch and coworkers [27] investigated the increased risks of obesity in DES daughters compared to non-exposed daughters and they also examined variables such as timing of in utero exposure to DES, dose and vaginal epithelial changes. The RR ratios comparing in utero DES-exposed vs. non-exposed women (offspring) and their obesity (BMI cutoff at 25) varied from 1.01 to 1.14 and the RR values for the low and high dose DES exposure cohort were 1.14 and 1.03, respectively. These results obtained for a potent estrogenic compound showed minimal effects and do not support the hypothesis that estrogenic EDC exposure in utero induces obesity in female offspring.

Animal models have been used extensively in endocrine disruptor research and in some cases observations in animal models have spurred research on the corresponding human health effects. However, the correlation between the observed endocrine-mediated responses in humans and laboratory animal models is compound, response, species and strain specific and this is routinely observed for other structurally diverse toxicants/pharmaceuticals [28,29]. There is extensive animal model data demonstrating that DES-induced reproductive tract abnormalities induced by DES in humans are also observed in rodents [25,26,30]. DES also enhances mammary tumor development in carcinogen-induced rat mammary tumor models [20] and in utero exposure of female AC1 rats to DES decreased the time-to-tumor formation and increased the incidence of mammary tumors [31]. In contrast, the DES-induced obesity in mice [25,26], which has been used as evidence to support the hypothesis that EDCs are obesogens, is not observed in DES daughters [27] suggesting that animal models of DES do not necessarily predict some human responses.

2.2. PCBs and DDE and breast cancer in women

The hypothesis that EDCs such as PCBs, DDE and other estrogens may contribute to the increasing incidence of breast cancer in women [3] was initially based on two small studies in Connecticut and New York [1,2]. These studies showed that polychlorinated biphenyls (PCBs) and 1,1′-bis(p-chlorophenyl)-2,2-dichloroethylene (DDE) were increased in breast cancer patients compared to control individuals. These observations triggered a worldwide investigation of the expression and levels of PCB mixtures and individual congeners and DDE in mammary tumors and tissues and serum. The results demonstrated that PCB and DDE levels were not elevated in breast cancer patients vs. controls although in some studies levels of a few individual congeners were increased or decreased in these groups [32–34]. In capacitor workers (females) highly exposed to commercial PCB mixtures the overall breast cancer incidence was reduced [35] in females suggesting that this class of organochlorine compounds do not play a role in mammary carcinogenesis.

In laboratory animal studies, there is evidence that lower chlorinated PCB mixtures such as Aroclor 1221 (21% by weight of chlorine) and some individual PCB congeners exhibit estrogenic activity in vivo (rodent) or in vitro [36,37]. However, studies in Sprague–Dawley rats showed that the higher chlorinated Aroclor 1260 PCB mixture inhibited spontaneous mammary tumor development in these animals [38]. Among the commercial