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Obesogenic effects of endocrine disruptors, what do we know from animal and human studies?

Marijke de Cock *, Margot van de Bor

VU University, Department of Health and Life Sciences, Faculty of Earth and Life Sciences, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands

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ABSTRACT

Background: Hormonal actions and activation of receptors involved in adipogenesis and brain development during the prenatal period may be affected by exposure to certain chemicals. Experimental studies have shown that amongst others polychlorinated biphenyl (PCB)-153 and dichlorodiphenyltrichloroethane (DDT) may have obesogenic effects in prenatally exposed mice.
Objective: To provide an overview of five classes of chemicals which have frequently been indicated as potential obesogens, and to discuss the evidence available regarding early life exposure to these compounds and overweight later in life.
Methods: Pubmed was systematically searched for publications which related early life exposure to endocrine disrupting chemicals (EDCs) to growth parameters later in life. We included 19 studies, which were published from 1995 and onwards.
Results: Both positive and negative associations are observed between early life exposure and weight or height at various ages, including as early as 14 months, as well as until 20 years of age. In none of the included studies negative associations between perinatal exposure to EDCs and body mass index (BMI) were found and in several studies a positive association was observed. Dose–response relations appear to be non-monotonic.
Conclusion: For certain EDCs, early life exposure may be associated with weight homeostasis later in life, however not necessarily in an obesogenic direction. More sensitive measures of adiposity as well as long-term follow-up are warranted for future studies.

1. Introduction

The prevalence of obesity continues to grow worldwide, presenting governments and health care organizations with a major challenge. Though at first obesity seemed to occur predominantly among adults, it is clear now that increasing numbers of children have to deal with the health consequences and social stigma of being overweight (Wang and Lobstein, 2006). In 2002 a review by Baillie-Hamilton was published which showed remarkable similarities between the obesity epidemic and the production of chemicals from 1930 and onwards (Baillie-Hamilton, 2002). Also in experimental studies it was showed that various chemicals had obesogenic effects. Female progeny of rats exposed to polychlorinated biphenyl (PCB)-153 experienced accelerated growth compared to controls (Sitarek and Gralewicz, 2009). PCB-153 furthermore stimulated adipogenesis in 3 T3-L1 adipocytes (Taxvig et al., 2012). Body weight of mice was affected after in utero exposure to a mixture of chemicals, including the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT), however dose–response was non-monotonic, with results for higher doses often being opposite from what was observed for lower doses (Palanza et al., 2001). Moreover, exposure of mature adipocytes to dichlorodiphenyldichloroethylene (DDE), the metabolite of DDT, resulted in increased leptin release (Howell and Mangum, 2010), a hormone which has been associated with fetal growth (Mellati et al., 2010).

It has become clear that certain compounds may interfere with the function of hormones (endocrine disrupting chemicals, EDCs), including estrogen, testosterone, and thyroid hormones (reviewed by Bergman et al. (Bergman et al., 2013)), which are involved in various processes in adults, but also in brain development early in life (Ahmed et al., 2008; Weiss, 2012). These hormones have also been associated with weight homeostasis, both early in development and later in life. Estrogens, for example, reverse weight gain often experienced by post-menopausal women (Jones et al., 2000). Moreover in men who are treated for prostate cancer and in women who are treated for polycystic ovary syndrome with anti-androgenic therapy, weight gain is observed (Grün and Blumberg,

Abbreviations: BFR, brominated flame retardant; BPA, bisphenol A; CMR, carcinogenic, mutagenic, or toxic for reproduction; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, di-2-ethylhexyl phthalate; EDC, endocrine disrupting chemical; HBCD, hexabromocyclododecane; HCB, hexachlorobenzene; MEHP, mono-ethylhexyl phthalate; PBT, persistant, bioaccumulative, and toxic; PCB, polychlorinated biphenyl; PBDE, polybrominated diphenyl ether; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PPAR, peroxisome proliferator-activated receptor.

* Corresponding author. Tel.: +31 20 59 83588.
E-mail address: m.de.cock@vu.nl (M. de Cock).

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2009; Jones et al., 2000). EDCs may interact with estrogen receptors, but may also affect aromatase activity. Aromatase is an enzyme which converts testosterone to 17β-estradiol. Developmental exposure to estradiol EDCs has been found to decrease expression of the aromatase gene (CYP19a1b) in the brain of male rainbowfish (Shanthanagouda et al., 2013). Decreased aromatase activity was however also observed in male rats prenatally exposed to a PCB-mixture (Hany et al., 1999). Other studies also suggest that aromatase activity may be affected by phthalates (Lovekamp and Davis, 2001), DDE (Wojtowicz et al., 2007), and various pesticides (terbuthylazine, propiconazole and prothioconazole) (Kjeldsen et al., 2013), although findings need to be substantiated.

EDCs may also interfere with thyroid hormone (TH) receptors as well as transport proteins for TH. Some isoforms of polybrominated diphenylethers (PBDEs) have been shown to exert inhibiting effects for binding of triiodothyronine to the TH receptor (Rubin and Soto, 2009). PBDE metabolites may furthermore bind to the transport protein transthyretin, resulting in displacement of thyroxine (Meerts et al., 2001). This has also been observed for perfluorinated alkyl acids, such as PFOS and PFOA (Weiss et al., 2009). This has been however predominantly shown in vitro.

Endocrine disruptors may furthermore promote obesity through peroxisome proliferator-activated receptor (PPAR) α and γ. Activation of PPARα stimulates lipid mobilization, but may indirectly also be obesogenic as prenatal activation may result in low birth weight, a known risk factor for obesity later in life. There are several options through which EDCs may promote obesity through PPARγ. Usually a ligand is needed for PPARγ to bind co-activators, release co-repressors, decondensate the chromatin and activate transcription (Janesick and Blumberg, 2011a). However post-translational modifications, such as phosphorylation, may activate PPARγ in the absence of a ligand (Perissi et al., 2010). EDCs may furthermore cause multipotent stromal cells (MSCs), cells which can differentiate into various tissues, to predominantly differentiate into adipose tissue (Janesick and Blumberg, 2011a; Janesick and Blumberg, 2011b). This particular subset of MSCs expresses PPARγ (Tang et al., 2008). This has in particular been found for organotins such as tributyltin (TBT).

What also needs to be considered is that PPAR agonists and their metabolites may activate multiple PPAR isoforms. Bis(2-ethylhexyl) phthalate (DEHP), an EDC from the phthalate class, may activate PPARα, however its metabolite mono (2-ethylhexyl)phthalate (MEHP) may activate PPARγ (Feige et al., 2007; Hurst and Waxman, 2003). And though lipid mobilization induced by PPARα activation requires continuous exposure, PPARγ may only need a single or episodic exposure to establish its effects in adipose tissues (Grün and Blumberg, 2009). Recent research has also indicated potential for perfluorinated alkyl acids, such as perfluorooctane sulfonate (PFOS), to interfere with PPAR by inducing expression of PPARγ genes in mouse neonatal brain after prenatal exposure (Wan Ibrahim et al., 2013).

Regulation of energy balance is a basic concept in the aetiology of obesity. Several factors control appetite and energy expenditure, which are all integrated in the hypothalamic–pituitary–adrenal (HPA) axis. The hypothalamus, and in particular the arcuate nucleus of the hypothalamus (ARH), is the centre for energy balance and appetite regulation.

Not much is known on developmental exposure to EDCs in relation to later appetite regulation. Chemicals may disrupt actions of hormones related to energy balance, e.g. leptin and insulin. It is clear that both leptin and insulin play important roles in development of feeding circuits which are comparable to sex steroid hormones with regard to the development of sexually dimorphic circuits (Bouret and Simerly, 2004). Rats injected with insulin between embryonic day 15 and 20 (term is 22 days) were significantly more obese at 50 days of age (Jones and Dayries, 1990). In leptin-deficient mice also ARH circuit formation was affected (Bouret et al., 2004). Leptin is also considered a regulator of fetal growth (Mellati et al., 2010) and low leptin levels at birth have been associated with a higher risk for obesity and diabetes (Martin-Gronert and Ozanne, 2005).

Early life exposure to these toxicants may have different effects than exposure in adulthood, as perturbations during stages of developmental plasticity may give rise to more profound long-lasting effects (Newbold, 2010). As endocrine disruption early in life seems to be a plausible mechanism which may predispose children to obesity, the aim of this study was to create an overview of six classes of chemicals which have frequently been indicated as potential obesogens in observational studies, and to discuss the evidence available regarding early life exposure (i.e. during the prenatal or early postnatal period) to these compounds and overweight later in life.

2. Methods

Articles were considered relevant when they determined effects of either dioxin-like compounds, non-dioxin like compounds, organochlorine pesticides, brominated flame retardants, phthalates or perfluorinated alkyl acids on growth and physical development in humans. PubMed was therefore systematically searched for publications by means of the following terms relating to exposure: chemical exposure, endocrine disruption (prenatal) environmental exposure, pesticides, bisphenol a (BPA), brominated flame retardant, DDE, DDT, hexachlorobenzene (HCB), organochlorines, organotin, perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), phthalates, polybrominated diphenyl ethers (PBDE), and PCB. Each of these terms was combined with the following terms relating to growth: obesity, overweight, fat, growth, anthropometry, cohort studies obesity, cohort studies overweight. In total 2832 publications were retrieved.

Articles were only considered when exposure was determined during pregnancy (or extrapolated to the period of pregnancy), or when it was measured in breast milk. Furthermore publications had to be written in English. Reference lists of articles included from the initial search were also searched for relevant publications. In total 19 publications of observational studies were included.

3. Results

An overview of observational studies included is given in Table 1.

3.1. Organotins

Organotins are characterized by a tin atom which is bound to an organic chain. The most common varieties are tributyltin (TBT) and triphenyltin (TPT) which are generally found in wood preservatives and antifouling boat paints. Due to their organic chain, they are hydrophobic and they therefore bioaccumulate. Human exposure occurs mainly through diet, in particular through sea food (Fent, 2003).

Though observational studies are not available, obesogenic characteristics of TBT in particular have been well documented in experimental studies. Prenatal exposure to this compound in mice has been associated with adiposity at later age (Grun et al., 2006). Furthermore, MSCs derived from the adipose tissue of these mice showed increased commitment to the adipocyte lineage compared to controls (Kirchner et al., 2010), at levels comparable to the tolerable daily intake of humans (Chamorro-Garcia et al., 2013). Differentiation of pre-adipocytes into adipocytes was increased by TBT exposure in a dose and time dependent manner (Bastos Sales et al., 2013; Pereira-Fernandes et al., 2013). Moreover, these effects may be heritable as Chamorro-Garcia et al. observed these results in both the F2 and F3 generation of exposed mice (Chamorro-Garcia et al., 2013). Gender-specific results have been reported, with effects on fat mass lasting longer in male mice than in female mice after prenatal exposure to TBT at human relevant levels (Penza et al., 2011).