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Annales d'Endocrinologie xxx (2017) xxx–xxx

Annales d'Endocrinologie
Annals of Endocrinology

Klotz Communications 2017: From the shortest to the tallest

Endocrine disrupting chemicals and growth of children

Perturbateurs endocriniens et croissance des enfants

Jérémie Botton [a,b,*], Manik Kadawathagedara [a], Blandine de Lauzon-Guillain [a]

[a] *Inserm, UMR1153 epidemiology and biostatistics Sorbonne Paris Cité center (CRESS), Team "early origin of the child's health and development" (ORCHAD), Paris Descartes university, Paris, France*

[b] *Faculty of pharmacy, université Paris-Sud, université Paris-Saclay, 92296 Châtenay-Malabry, France*

Abstract

According to the "environmental obesogen hypothesis", early-life (including *in utero*) exposure to endocrine disrupting chemicals (EDCs) may disturb the mechanisms involved in adipogenesis or energy storage, and thus may increase the susceptibility to overweight and obesity. Animal models have shown that exposure to several of these chemicals could induce adipogenesis and mechanisms have been described. Epidemiological studies are crucial to know whether this effect could also be observed in humans. We aimed at summarizing the literature in epidemiology on the relationship between EDCs exposure and child's growth. Overall, epidemiological studies suggest that pre- and/or early postnatal exposure to some EDCs may increase the risk of overweight or obesity during childhood. In that review, we present some limitations of these studies, mainly in exposure assessment, that currently prevent to conclude about causality. Recent advances in epidemiology should bring further knowledge.

Keywords: Environment; Epidemiology; Growth; DOHaD; Endocrine disrupting chemicals; Obesity

Résumé

Selon l'hypothèse de l'existence d'obésogènes environnementaux, des expositions à des perturbateurs endocriniens (PE) pendant la période précoce de vie (incluant la période intra-utérine) pourraient perturber les mécanismes impliqués dans l'adipogenèse et le stockage énergétique et ainsi, augmenter la susceptibilité au surpoids et à l'obésité. Des modèles animaux ont montré que des expositions à plusieurs de ces chimiques pouvaient stimuler l'adipogenèse et des mécanismes ont été décrits. Les études épidémiologiques sont essentielles pour savoir si cet effet est également observé chez l'homme. Nous avions pour objectif de résumer la littérature en épidémiologie sur la relation entre l'exposition à des PE et la croissance des enfants. Globalement, les études épidémiologiques suggèrent que certaines expositions pré- ou postnatales pourraient augmenter le risque de surpoids ou d'obésité durant l'enfance. Dans cette revue, nous présentons également des limites de ces études, principalement concernant l'évaluation de l'exposition, qui empêchent pour le moment de conclure à la causalité de ces associations. Des avancées récentes en épidémiologie devraient permettre d'améliorer la connaissance dans ce domaine.

Mots clés : Environnement ; Épidémiologie ; Croissance ; Origine développementale de la santé et des maladies ; Perturbateurs endocriniens ; Obésité

1. Background

The prevalence of overweight and obesity has increased during the last decades, including in children [1]. During the same period of time, an increase in the synthesis of chemicals has been observed [2]. In this context, several studies have been carried out to explore the potential causality between exposure to chemicals and overweight or obesity. According to the "environmental obesogen hypothesis", early-life (including in utero) exposure to endocrine disrupting chemicals (EDCs) may disturb the mechanisms involved in adipogenesis or energy storage, and thus, may increase the susceptibility to overweight and obesity [3]. In fact, animal models have shown that exposure to EDCs in early life could induce adipogenesis [4–7] and mechanisms

* Corresponding author at: Inserm UMR 1153–Équipe Orchad, 16, avenue Paul-Vaillant-Couturier, 94807 Villejuif cedex, France.
E-mail address: jeremie.botton@inserm.fr (J. Botton).

http://dx.doi.org/10.1016/j.ando.2017.04.009
0003-4266/

Please cite this article in press as: Botton J, et al. Endocrine disrupting chemicals and growth of children. Ann Endocrinol (Paris) (2017), http://dx.doi.org/10.1016/j.ando.2017.04.009

have been described [8–10]. Epidemiological studies are crucial to know whether this could be also true in humans. A number of recent pregnancy or birth cohort studies offered the possibility to explore the environmental determinants of growth and obesity very early in life, at specific critical windows and prospectively.

The most studied EDCs in epidemiology are bisphenol A (BPA), phthalates and persistent organic pollutants (POPs), including organochlorinated pesticides, polychlorinated biphenyls (PCBs) and dioxins, all being ubiquitous contaminants. Phthalates are used in many consumer products [11]: low molecular weight phthalates are mainly used in personal care products (perfumes, lotions, cosmetics) or as coating for pharmaceutical products to provide timed releases; high molecular weight phthalates are used as plasticizers in polyvinylchloride floor and wall covering, food packaging, and medical devices. BPA is mainly used to produce polycarbonate plastics and epoxy resins which are found in many consumer products, including toys, polycarbonate water bottles and food storage containers [12]. POPs persist in the environment, and accumulate in adipose tissue. They include chemicals that were widely used as pesticides (e.g. dichlorodiphenyltrichloroethane, DDT, its metabolite p,p'-dichlorodiphenyldichloroethylene, p,p'-DDE, hexachlorobenzene, HCB) and in industrial processes (PCBs). In spite of the ban of most of these chemicals [13], due to their persistence, the general population is still exposed [14,15].

We aim at summarizing the literature in epidemiology on the relationship between EDC exposure and child's growth.

2. Results

The epidemiological studies on the relationship between BPA and overweight or obesity in children are inconclusive. Results from cross-sectional studies generally showed that higher urinary BPA concentrations are positively associated with obesity [16–20], but the direction of the relationship cannot be established using this design. Few prospective cohort studies examined early-life BPA exposure in association with later childhood body mass index (BMI) [21–25]. In two studies, higher prenatal BPA exposure was associated with higher BMI or weight for height among children [23,24], while two others reported lower BMI with higher earlier childhood exposure [21,22]. The most recent study found that higher BPA concentrations in children's urine were associated with increased BMI z-score at 4 years of age, whereas prenatal BPA concentrations were negatively associated with BMI and adiposity measures in girls and positively in boys [25].

Some epidemiological studies showed that prenatal or childhood phthalate exposures were associated with child adiposity, but overall the associations remain inconsistent [26]. Most of the studies that have assessed the association with childhood exposure were cross-sectional [27–30]. Low-molecular weight phthalates exposure (incl. diethyl-phthalate, DEP) in girls aged 6–8 years was positively associated with changes in BMI and waist circumference after several years [31]. Teitelbaum et al. main findings were the associations of the monoethylphtalate MEP (i.e. DEP metabolite) at 6–8 years with BMI and waist circumference one year later among overweight children [32]. One prospective study reported negative associations between prenatal urinary concentrations of metabolites of high molecular weight phthalates and body mass index (BMI) gain during childhood in boys [33]. In another study, prenatal concentrations of non-DEHP metabolites were associated with lower BMI in boys at 5 ears [34]. In a pooled analysis of three prospective cohort studies representing 707 US children, Buckley et al. reported a sex-specific association between MEP during pregnancy and BMI at 4–7 years, which was negative in girls and positive (although not statistically significant) in boys [35]. In a population of boys, maternal urinary concentrations of MEP was positively associated with weight growth velocity from two years onwards, with weight at 3 and 5 years and with BMI at five years [36]. A study relying on a multi-pollutants analysis did not find any association between prenatal phthalates exposure and BMI at 7 years [37].

The persistent organic pollutants (POPs) were the most studied chemicals among early-life exposures that may be obesogenic. Several longitudinal birth cohort studies have examined the relationship between prenatal exposure to POPs and child growth or obesity. Prenatal DDT and DDE exposure has been positively associated with BMI in infancy or childhood [38–43]. In a pooled analysis of 7 European birth cohorts, prenatal p,p'-DDE was associated with increased infant growth [44]. Prenatal HCB exposure has been positively associated with rapid growth in the first 6 months of life and obesity in infancy [39] and childhood [45,46]. Cord blood concentration to another organochlorine pesticide, chlordecone, has been shown to be associated with a higher BMI in boys at 3 months, due to higher weight growth and lower height growth, and in girls at 8 and 18 months, mostly due to lower height, whereas postnatal exposure was associated with lower height, weight and BMI at 3, 8 and 18 months, particularly in girls [47]. In a pooled analysis of three European birth cohorts, perinatal exposure to dioxin and dioxin-like compounds was associated with increased early infant growth, and increased BMI in school age girls [48]. The elevated BMI was due to higher weight and not lower height, and corresponded to an increased risk of overweight. Findings for the association between prenatal PCB exposure and childhood obesity have been less consistent [38–40,42,49–51]. In a pooled analysis of 7 European birth cohorts, postnatal PCB-153 was associated with decreased infant growth [44].

3. Conclusion

Overall, the epidemiological literature suggests that pre and/or early postnatal exposure to some EDCs may increase the risk of overweight or obesity during childhood. Several differences in the associations have been described according especially to the period of exposure and to the age and sex of the child. Only few studies reported whether the association with BMI was mainly due to an association with weight or height growth.

According to the EDCs considered, limitations in exposure assessment have to be highlighted. First, POPs accumulate in the body over the lifecourse, are stored in the adipose tissue and it is

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