Endocrine disruptors

Environmental disruptors: New diabetogens?

Perturbateurs endocriniens environnementaux : de nouveaux diabétogènes ?

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A B S T R A C T

The prevalence of type-2 diabetes has dramatically increased worldwide during the last few decades. While lifestyle factors (sedentary, noxious food), together with genetic susceptibility, are well-known actors, there is accumulating evidence suggesting that endocrine disrupting chemicals (EDCs) may also play a pathophysiological role in the occurrence of metabolic diseases. Both experimental and epidemiological evidence support a role for early and chronic exposure to low doses of chemical pollutants with endocrine and metabolic disrupting effects. Most are present in the food chain and accumulate in the fat mass after absorption. In rodents, bisphenol A stimulates synthesis and secretion of pancreatic β cells and disturbs insulin signaling in liver, muscle and adipose tissue through epigenetic changes leading to insulin resistance and β cell impairment. In humans, epidemiological reports show statistical link between exposure to pesticides, polychlorinated bisphenols, bisphenol A, phthalates, dioxins or aromatic polycyclic hydrocarbons or heavy metals and DT2 after acute accidental releases or early in life and/or chronic, low doses exposure. More prospective, longitudinal studies are needed to determine the importance of such environmental risk factors.

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R É S U M É

La prévalence du diabète de type 2 a considérablement augmenté dans le monde, sans qu’il soit possible d’expliquer cette pandémie uniquement par une prédisposition génétique et/ou des changements de style de vie (sédentarité et suralimentation). Des arguments expérimentaux et épidémiologiques soutiennent un rôle pour l’exposition à des polluants chimiques perturbateurs endocriniens (PEs) interférant avec les systèmes de régulation hormonaux critiques pour l’hémostasie énergétique. Beaucoup sont présents dans la chaîne alimentaire et, après absorption, sont séquestrés dans le tissu adipeux. Chez les rongeurs, l’exposition au bispénonal A altère la synthèse et la sécrétion d’insuline dans les cellules bêta-pancréatiques, ainsi que la signalisation de l’insuline dans le foie, le muscle

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1. Introduction

The current prevalence of diabetes and obesity is unprecedented. In 2013, the World Health Organization (WHO) reported that 347 million people suffer from diabetes all over the world (90% of them have type-2 diabetes) [1,2], whereas the same organization predicted earlier in the 2000s a number of 330 million people with diabetes in 2030 [3]. More recently, a report of the International Diabetes Federation (IDF) estimated this number to 382 million people in the world, for a prevalence of 8.3% [4].

Based on data extracted from the US Centers for Disease Control and Prevention (CDC) between 2005 and 2008, and from IDF Diabetes Atlas, 24.4 million American people beyond 20 years of age (comparative prevalence of 9.2%) have been diagnosed or undiagnosed with diabetes [4,5] in France, more than 3.3 million (comparative prevalence of 5.4%) people have diagnosed for diabetes [5]. The total direct medical costs and indirect costs (disability, work loss, premature death) associated with diabetes in the US during 2007 was $174 billion [4], and more recently $245 billion (with an individual cost of $9800 per year) [4,5], and €15 billion in France (with an individual cost of €5406 per year) [1,5]. Moreover, 31.2 million American people and 3.7 million French people (comparative prevalence of 12.3% and 6.6%, respectively) in this age category are estimated to have pre-diabetes, which is a predictor for the development of diabetes [4,5]. Furthermore, the prevalence of obesity worldwide had doubled since 1980 [1], and tripled in children and adolescents between 2 and 19 years of age. This trend is also apparent in preschool children between 2 and 5 years of age [6], and more recently in developing countries.

The reasons for this rapid increase in diabetes and obesity remain unclear. Excess caloric consumption and a sedentary lifestyle are undoubtedly key causal factors for obesity and diabetes. However, there is growing interest in the contribution of “non-traditional” risk factors as industrial micronutrients, gut microbiome changes and environmental endocrine disrupting chemicals, to the etiology of metabolic diseases. Indeed, increased body weight has also been reported in pets and laboratory animals over the past decades and could not be explained by changes in dietary patterns and/or physical activity. While the development of synthetic chemistry has drastically improved our quality of life, research addressing the role of environmental chemicals in diabetes and obesity has rapidly expanded in the past several years, suggesting that environmental disruption of metabolism could constitute the “paradox of progress” as cited by Neel and Sargis [7]. In 2011, the US National Institute of Environmental Health Sciences (NIEHS) organized a state-of-the-science workshop and concluded that the existing literature provided plausibility, varying from suggestive to strong, that exposure to environmental chemicals with endocrine and metabolic disrupting effects may contribute to the epidemic of diabetes and/or obesity [8].

There is also growing evidence that exposure to these endocrine disrupters such as xenoestrogens, when occurring during critical periods of embryonic development, could cause permanent changes by programming gene expression and unexpected effects on metabolism. These observations could be compared with the human unwilling experiment of fetal exposure to diethylstilbestrol (DES), a potent estrogen compound used in the prevention of miscarriages until 1975. An increased risk of different pathologies, including genital malformations, infertility and hormone dependent cancers have been reported in these exposed children [9]. More recently, DES exposure was related to obesity in mice, with the same phenotype than previously described in children with in utero growth retardation who exhibited a low birth weight followed by a “catch-up” period resulting in increased body weight (also known as thrifty phenotype, the best predictor of insulin resistance) [9]. This concept is quite similar to the one proposed by David Barker [10], based on the deleterious fetal nutritional environment leading to intra-uterine growth retardation and influencing the later occurrence of adult metabolic syndrome, as well as obesity, type-2 diabetes and cardiovascular diseases, known as the Developmental Origin of Health and Disease (DOHaD) hypothesis, underlying the critical window of fetal period for exposure to EDCs. This DOHaD hypothesis can be now extended to many deleterious fetal environmental factors such as, maternal stress, noxious diet, toxic exposure, hyperglycemia, which could influence growth in utero and postnatal development through epigenetic modifications [11]. Indeed, there are both in vivo and in vitro experimental data and epidemiological evidences that support the hypothesis that exposure to endocrine and metabolic disrupting pollutants during critical periods could be involved in the pandemic of type-2 diabetes.
2. Experimental data

DT2 is characterized by increased insulin resistance and pancreatic beta cell dysfunction. Obesity is the main environmental factor driving the increased incidence of DT2. Obesity, especially visceral or central obesity, is associated with insulin resistance that promotes β cell proliferation leading to hyperinsulinemia, metabolic syndrome and later to DT2. Endocrine and metabolic disrupting pollutants are able to facilitate the occurrence of central obesity as reviewed in [12]. However, obesity is neither necessary nor sufficient to cause T2D. We will focus here on chemical pollutants able to directly influence insulin resistance and/or pancreatic β cell function deterioration.

2.1. In vivo animal studies

A number of chemicals including persistent organic pollutants such as dioxins, furans, chlorinated pesticides, polychlorinated biphenyls (PCB) flame-retardant polybrominated diphenyl ethers, organochlorine bisphenyls, perfluorinated acids (PFOS, PFAS), non-persistent pollutants such as phthalates, bisphenol A or tributyltin, or heavy metals such as cadmium, arsenic or mercury, have been shown to induce biological effects that alter glucose homeostasis after acute or chronic exposure in mice and rats. Adult mice exposed to TCDD (Seveso Dioxin) exhibited reduced glucose-stimulated insulin release, an effect absent in AhR (Aryl hydrocarbon receptor)-null mice [13]. Concerning pesticides, atrazine promotes insulin resistance [14] and malathion exposure results in increases in both glucose and insulin levels in rats [15]. PCB126 and PCB77 were shown to impair glucose tolerance with induction of insulin resistance when coupled with a low-fat diet [16]. PCB mixture aroclor 1254 induced insulin resistance in both lean and diet-induced obese states [17]. Aroclor1260 administered to mice fed a high-fat diet altered carbohydrate metabolism at multiple levels, highlighting the additive role of dietary metabolic stressors in the effects of EDCs [18].

While acute exposure of male mice to BPA led to a rapid increase in plasma insulin and in a corresponding decrease in plasma glucose, chronic exposure to BPA was found to induce hyperinsulinemia and also to reduce insulin sensitivity, suggesting that BPA may be a diabetogenic factor per se. Interestingly, the impairment in insulin action occurred despite an increase in β-cell insulin content and especially appeared when mice were exposed to BPA orally or by subcutaneous injection [19]. One explanation is that BPA operates through several pathways and mechanisms that independently increase insulin synthesis, while simultaneously inducing peripheral insulin resistance in adipose tissue, liver and especially in skeletal muscle due to impairments of insulin signaling [20]. Furthermore, insulin resistance observed after chronic exposure to BPA may consist in an adaptive cruise to higher insulin levels in order to limit hypoglycemia [21]. Chronic exposure to BPA led also to changes in whole-body energy homeostasis, by a direct effect of BPA on the central nervous system responsible for lower energy intake and for lower energy expenditure [20]. These results are similar to those observed in experimental models exposed with TCDD, diethylhexyl phthalate (DEHP) or tributyltin, an organotin used as biocide in anti-fouling paint in order to prevent the settling of organisms on the hulls of large ships. Cadmium exposure has been shown to promote glucose intolerance with a specific reduction in adipocyte expression of GLUT4 [22] and in vivo exposure to arsenic promotes glucose intolerance with concordant insulin resistance [23].

2.2. Perinatal exposure

Results from experiments using animal models have demonstrated that nutritional changes during pregnancy can directly affect the programming of metabolically active tissues and can induce type-2 diabetes, in their offspring [24]. In addition to nutritional changes, exposure to EDCs in animal models also alters glucose homeostasis in mothers and their offspring when they become adults. For example, prenatal exposure of mice to DES resulted in a significant decrease in body weight during treatment, which was followed by a “catch-up” period around puberty, and then finally resulted in a significant increase in body weight associated with an increase in the percent of body fat after two months of age. Increased body weight was maintained throughout adulthood and DES-treated mice exhibited higher levels of adiponectin, leptin and IL-6, as well as altered glucose levels [9]. Perinatal DDT exposure in rats impairs thermogenesis and the metabolism of carbohydrates and lipids, which may increase susceptibility to the metabolic syndrome in adult female offspring [25]. Exposure to low doses of PFOS during gestation and early postnatal development resulted in glucose intolerance and insulin resistance [26]. In a rat model, females exposed to phthalates (DEHP) throughout gestation and perinatal development, exhibited in offspring, hyperglycemia in the presence of reduced insulin levels and reduction in β cell mass [27]. Results with perinatal exposure to BPA are controversial. While initial studies reported that oral exposure to BPA during pregnancy and lactation increased the body weight of adult male and female offspring [28], more recent reports showed very mild phenotypes. These discrepancies between the studies may be explained by all the differences in experimental design, dosage or both [19]. More recently, effects of BPA exposure during mice pregnancy were shown to mimic the effects of a high-fat diet altering glucose and lipid metabolism [29]. In any case, BPA exposure during a short time during pregnancy may affect the metabolic programming (weight and glucose metabolism) of offspring later in life, but also the metabolic state of the mother in the long-term.

2.3. In vitro experimental studies

Several studies reported that organic pollutants could enhance insulin resistance in vitro by a direct action on adipocytes. For example, cultured and differentiated mouse adipocytes 3 T3-L1 cells exposed to a mixture of persistent organic pollutants had an impaired response to
insulin (especially with organochlorine pesticides) and exhibited a down regulation of insulin-induced gene-1 (Insig-1) and Lpin1, two key regulators of lipid metabolism [30]. Exposure of mouse and human cultured cells to phthalates, especially mono-(2-ethylhexyl)-phthalate (MEHP) and monobenzyl-phthalate (MBzP), led to activation of PPARα and PPARγ, and then to fatty acid oxidation and to a strong adipocyte differentiation [31]. Despite controversial data, some dioxins (especially 2,3,7,8-tetra-chlorodibenzo-p-dioxin, TCDD) were demonstrated to impair glucose uptake by the adipose tissue and the pancreas (due to a reduction in GLUT4 and glucokinase expression), as well as insulin secretion [32]. Bisphenol A (BPA), or 2,2′-bis-4-hydroxyphenyl-propane, is one of the highest volume chemicals produced worldwide. It was first designed in the late 1890s as a synthetic estrogenic compound and was investigated for potential commercial use in the 1930s; although its estrogenic activity had been confirmed, BPA has been substituted for DES, which exhibited far more potent estrogenic effects [33]. Due to its heat resistance and its elasticity, a use for BPA was identified in the plastics industry during the 1950s. It is currently used in the manufacturing of polycarbonate plastic and epoxy resins, notably contained in bottles, food storage containers, and dental sealants [34], explaining why most people have detectable levels of BPA in their urine [35] and in their serum [36]. Although much of the concern regarding BPA toxicity focused on reproductive health and development, more recently DES and BPA were shown to induce in freshly isolated islets of Langerhans a rapid glucose-induced Ca²⁺ signal, which is a key messenger responsible for insulin secretion [37]. Exposure to a single low dose of BPA decreased blood glucose levels and simultaneously increased serum insulin levels, but led to post-prandial hyperinsulinemia leading to insulin resistance, especially in peripheral tissues such as adipocytes, liver and skeletal muscle [19]. The augmentation in β-cell insulin content and release after BPA exposure appears to be a direct result of its estrogenic properties, as these effects were not observed in ERα-knockout animals [19]. However, these rapid actions of BPA occurred via a non-classical estrogen-activated pathway, as they were not counteracted by the antiestrogen fulvestrant [38], involving probably GPER [39] and/or ERβ [40] and/or estrogen-related receptor γ (ERRγ) [41]. Human adipocytes have been demonstrated to be also an important target of BPA, which could reduce adiponectin production and secretion [42] and enhance adipocyte differentiation and lipid accumulation [43], leading to an insulin-resistant state that may result in type-2 diabetes when combined with a genetic predisposition, an excess caloric consumption and/or a sedentary lifestyle.

2.4. Cellular and molecular mechanisms

However, effects of EDCs are not limited to interactions with ERs and PPAR. Indeed, EDCs are classically able to induce changes in gene expression that may persist throughout life, despite no change in DNA sequence, also known as epigenetic modifications, including DNA methylation, histone modifications and expression of non-coding RNAs (microRNAs, picoRNAs . . .). Multiple lines of evidences from animal models have established that epigenetic modifications due to in utero exposure to EDCs, especially DNA methylation, can induce alterations in gene expression that may persist throughout life [44,45]. The epigenetic effect of BPA was clearly demonstrated as maternal exposure to BPA shifted the coat color distribution of viable yellow mouse offspring toward yellow by decreasing Cpg methylation of the Agouti gene [44]. Thus, in utero and perinatal exposure to BPA may induce DNA hypermethylation and/or hypomethylation of several gene promoters, as well as histone modifications and expression of miRNAs, which may contribute to alter glucose metabolism and β-cell failure, as observed in type-2 diabetes. These non-genomic mechanisms may also be involved in the transgenerational transmission of this programmed defect [46,47], as previously described for reproductive tract abnormalities and subfertility induced by in utero exposure to DES [48]. Epigenetics represents likely the molecular link [49] between environmental factors and T2D as illustrated by fetal BPA exposure in rat, which results in glucokinase gene promoter hypermethylation, contributing to insulin resistance in adulthood [50] and in F2 generation [51].

3. Epidemiological evidence of diabetogenic pollutants

The current debate about the metabolic effects of EDCs is focused primarily on the results of in vitro experiments and on in vivo animal models. However, despite several strong arguments, the extrapolation of animal results to a hazard for human health remains difficult, as humans are daily exposed to a complex mixture of toxicants.

3.1. Accidental exposures

Initial data linking diabetes to environmental pollutants have come from epidemiological studies performed after acute and accidental releases of EDCs. The explosion of a chemical plant in Seveso, Italy, was responsible for a massive and acute release of dioxins in the summer of 1976; follow-up studies showed, several years after this environmental disaster, an increased risk of diabetes in exposed people, especially in women [52]. The study of military personnel exposed to dioxins contained in herbicide orange used by the US military program, Operation Ranch Hand, during the Vietnam War, revealed the same association between serum TCDD concentration and the prevalence of type-2 diabetes (relative risk [RR] = 1.5; [95% CI: 1.2–2.0]) [53]. Consumption of adulterated rice bran cooking oil in a group of Taiwanese, also known as the in Yu-cheng incident, was related to a higher prevalence in type-2 diabetes, especially in women (odds ratio [OR] = 2.1; [95% CI: 1.1–4.5]), due to a contamination with polychlorinated biphenyl ethers (PCBs), dioxins and furans [54]. Some recent observations were performed with indirect consumption of persistent organic pollutants (POPs) including organochlorine pollutants, heavy metals and metabolites of the insecticide DDT, despite its ban in 1972 because of its toxicity on fertility [55].
A major limitation of these studies using occupational cohorts is that in many cases, the exposure occurs many years before the analysis is undertaken; thus levels of POPs are usually estimated by questionnaires or by back calculation from serum or urine concentrations measured many years later, while the half-life of each pollutant may easily vary according to the conditions of sample preservation. Furthermore, most of these occupational studies focused on exposure to one EDC at a time, while the worker cohorts are usually exposed to a whole mixture of toxicants, often in large concentrations; therefore, the results could be confounded by exposure to other chemicals, so that they may not reflect the exact risk incurred by the general population.

3.2. Cross-sectional transversal studies

Epidemiological studies performed on non-occupational populations are very suggestive of an independent association between POPs exposure and diabetes. Nevertheless, they have been focused on individuals who live in heavily polluted areas (Scandinavia, Great Lakes), raising the matter of the control group that has been chosen [56]. Indeed, the diet could act as a confounder in establishing the causality between exposure and diabetes and between exposure and obesity, as most of those people (the cases as well as the controls) are daily exposed to POPs, via food intake and water drink. For this reason, the spectacular concordance between the evolution of diabetes prevalence in the United States and the national production of synthetic organic compounds should be carefully considered [7].

The data showing a link between EDCs exposure and diabetes in general population studies mainly comes from the US National Health and Nutrition Examination Survey (NHANES), which is an American food consumption database program that began in 1960 and was designed to assess the health and nutritional status of adults and children in this country. Since 1999, this program includes testing of blood and urine for an extensive number of chemicals and monitors yearly 5000 to 10,000 representative persons, with a cross-sectional analysis performed each two years. Those analyses showed that most participants had detectable blood and/or urine levels of several chemicals (in particular BPA) and that diagnosed or self-reported diabetes was strongly associated with exposure to PCBs, dioxins, p,p’-DDE, phthalates and also BPA (with an OR reaching 2.74; [95% CI: 1.44–5.23]) after adjustment for age, gender, body mass index and ethnicity [57,58]. However, it is interesting to notice that a recent systematic review showed that the positive correlation observed between EDCs exposure (in particular BPA or phthalates exposure) and diabetes was found only in the 2003/2004 NHANES survey or in pooled data that included the 2003/2004 survey [59,60]. Other cross-sectional studies among the world reported suggestive hints of strong association between diabetes and prediabetes and EDCs exposure [61,62].

3.3. Prospective, longitudinal studies

Recently, Sun et al. compared the prevalence of diabetes in US women from the Nurses’ Health Study (NHS an NHSII) according to their levels of BPA and phthalates assessed from blood and urine samples collected 5 to 10 years before [63]. After adjustment for BMI, they showed in this prospective, longitudinal case/control study, a positive correlation between urinary BPA and butylphthalate concentrations and incident type-2 diabetes in the premenopausal participants (NHSII), but not in the older NHS counterparts [63]. However, some several limitations with these epidemiological studies should be highlighted, as detailed by Magliano et al. [56]. As in any observational study, the association between EDCs exposure and diabetes does not establish causality. Furthermore, many of the above studies (excepted for the NHS and the NHSII) were designed to correlate diabetes prevalence with current EDCs levels, while their current levels may strongly differ from concentrations during disease development. Moreover, EDCs are usually highly correlated with each other, and it is not always possible to precisely determine the independent effect of each chemical compound when people are daily exposed to a whole mixture. Finally, the association between EDCs exposure and diabetes may be due to confounding by fat mass, as most of EDCs are stored in adipose tissue, and/or energy dense diet, especially sweet beverages from tinned cans, which contain a large amount of EDCs. Further higher levels of POPs were related to diabetes only in overweight patients, suggesting that EDCs exposure may have a synergistic effect with increased adipose tissue on the risk of type-2 diabetes [64]. An interesting case/control Canadian study compared recently menopausal obese women (BMI > 30 kg/m²). For similar age, BMI, and fat mass index metabolically healthy obese (MHO) women (30 to 40% of obese patients) showed less visceral adipose tissue, higher insulin sensitivity levels and a more favorable cardiometabolic profile than in metabolically abnormal (MAO) obese women. MHO was associated with lower plasma levels of several dioxin-like and non-dioxin-like persistent organic pollutants, suggesting that POPs should be considered as real risk factors for visceral obesity, insulin resistance, and DT2 [65].

4. Conclusion

Genetic predisposition and environmental factors such as overnutrition and sedentariness play key roles in the etiology of DT2. However, humans are daily exposed to a whole mixture of hormonally active chemicals that have additive actions and that must now also be taken into account as a serious risk factor for the development of type-2 diabetes, especially in developing countries where exposure to EDCs may still be high for decades to come. Thus, while extrapolation of animal results to human health could be hazardous, there are now numerous experimental studies performed with doses similar to those found in humans showing that many persistent or non-persistent organic pollutants present in our environment should be considered as endocrine and metabolic disrupters. They may represent the next risk factors for DT2 by acting at three levels, insulin resistance, obesity, and/or β cell function. Several epidemiological studies among the world suggested that there should be a strong
association of diabetes with exposure to common EDCs, especially for organic pollutants. Those observational studies analyzed one EDC at a time, rather than the whole mixture of EDCs to which individuals are daily exposed. Furthermore, this kind of study cannot demonstrate causality. Additional prospective, longitudinal studies are needed to definitively confirm or refute the link between EDCs exposure and type-2 diabetes. It is also necessary to identify biomarkers of duration and intensity of EDCs exposure and to recognize early induced molecular imprinting (epigenetic modifications) on liver, adipose tissue, pancreatic beta cells and muscle. Another key issue is that EDCs can exhibit worse effects at low doses (below those used for traditional toxicological studies) that are not predicted by effects at higher doses, especially BPA [66]. Finally, the relative meaning of such new factors in comparison with genetic and other environmental factors remains still to be determined. Meanwhile, the precautionary principle concerning EDCs exposure should be adopted in medical practice, especially during the most sensitive periods of life, such as infancy and pregnancy.

Disclosure of interest

The authors declare that they have no competing interest.

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