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Endocrine disruptors

Environmental endocrine disruptors: New diabetogens?

Perturbateurs endocriniens environnementaux : de nouveaux diabétogènes ?

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ABSTRACT

The prevalence of type-2 diabetes has dramatically increased worldwide during the last few decades. While lifestyle factors (sedentariness, 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 bisphenyls, bisphenol A, phthalates, dioxins or aromatic polycyclic hydrocarbides 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.

Mots clés :
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RÉSUMÉ

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'homéostasie énergétique. Beaucoup sont présents dans la chaîne alimentaire et, après absorption, sont séquestrés dans le tissu adipeux. Chez les rongeurs, l'exposition au bisphénol 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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squelettique et le tissu adipeux, entraînant des modifications épigénétiques programmant à distance résistance à l'insuline et/ou défaillance cellulaire β. Des études épidémiologiques humaines suggèrent un lien étroit entre exposition à certains pesticides, bisphénols polychorés, bisphénol A, phtalates, dioxines, hydrocarbures aromatiques polycycliques, métaux lourds et DT2, après des expositions accidentelles ou dans le cadre d'études transversales. Mais il est nécessaire de réaliser des études longitudinales prospectives, de mieux comprendre les mécanismes moléculaires et d'identifier des marqueurs précoces d'exposition chronique à faibles doses de ces molécules chimiques afin d'évaluer l'importance de tels facteurs de risque.

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 prediabetes, 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.

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