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Review

Endocrine disruptors: New players in the pathophysiology of type 2 diabetes?

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Abstract

The prevalence of type 2 diabetes (T2D) has dramatically increased worldwide during the last few decades. While lifestyle factors, such as decreased physical activity and energy-dense diets, together with genetic predisposition, are well-known actors in the pathophysiology of T2D, there is accumulating evidence suggesting that the increased presence of endocrine-disrupting chemicals (EDCs) in the environment, such as bisphenol A, phthalates and persistent organic pollutants, may also explain an important part in the incidence of metabolic diseases (the metabolic syndrome, obesity and T2D). EDCs are found in everyday products (including plastic bottles, metal cans, toys, cosmetics and pesticides) and used in the manufacture of food. They interfere with the synthesis, secretion, transport, activity and elimination of natural hormones. Such interferences can block or mimic hormone actions and thus induce a wide range of adverse effects (developmental, reproductive, neurological, cardiovascular, metabolic and immune). In this review, both *in vivo* and *in vitro* experimental data and epidemiological evidence to support an association between EDC exposure and the induction of insulin resistance and/or disruption of pancreatic β-cell function are summarized, while the epidemiological links with disorders of glucose homoeostasis are also discussed.

Keywords: Diabetes; Type 2 diabetes; Endocrine disruptors; Pollutants; Bisphenol A; Oestrogens

1. Introduction

The current prevalence of diabetes and obesity is unprecedented. In 2013, the World Health Organization (WHO) reported that 347 million people all over the world suffer from diabetes [90% of them with type 2 diabetes (T2D)] [1,2], whereas that same organization had predicted earlier in the 2000s that the number of people with diabetes would be 330 million in 2030 [3]! More recently, a report from the International Diabetes Federation (IDF) estimated this number to be 382 million people all over 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 the IDF Diabetes Atlas, 24.4 million Americans over 20 years of age (comparative prevalence of 9.2%) have diagnosed or undiagnosed diabetes [4,5]; in France, more than 3.3 million people (comparative prevalence of 5.4%) have a diagnosis of diabetes [4]. The total direct medical costs and indirect costs (disability, work loss, premature death) associated with diabetes in the US in 2007 was $ 174 billion [5] 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) [4,6]. Moreover, an estimated 31.2 million American people and 3.7 million French people (comparative prevalences of 12.3% and 6.6%, respectively) in this age category are thought to have prediabetes, a predictor for the development of diabetes [4,5].

Based on WHO statistics in 2011, the prevalence of obesity worldwide had doubled since 1980, 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 [7] and, more recently, in developing countries, too.

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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, such as environmental chemicals, micronutrients and the gut microbiome to the aetiologies of these health conditions. Indeed, increased body weight has also been reported in pets and laboratory animals over the past decades, and cannot be explained by changes in dietary patterns and/or physical activity. While developments in synthetic chemistry have radically improved our quality of life, research addressing the role of environmental chemicals in diabetes and obesity has rapidly expanded over the past several years, suggesting that environmental disruption of metabolism could constitute the "paradox of progress", as coined by Neel et al. [8]. 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 ranging from suggestive-to-strong that exposure to environmental chemicals may be contributing to the epidemics of diabetes and obesity [7]. Indeed, there are both *in vivo* and *in vitro* experimental data and epidemiological evidence to support such an hypothesis. Thus, the present review discusses the experimental data demonstrating links between chemical exposures and changes in insulin action/secretion, summarizes the epidemiological links with disorders of glucose homoeostasis, and highlights any gaps or flaws in the evidence.

2. Endocrine disruption and the oestrogen hypothesis

Endocrine-disrupting chemicals (EDCs) have been defined by the US Environmental Protection Agency (EPA) as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" [9]. EDCs can interfere with synthesis, secretion, transport, metabolism, binding actions and elimination, and mimic the occurrence of natural blood-borne hormones. EDCs include a wide variety of chemicals, such as pesticides, environmental pollutants, and compounds or components used in the plastics industry and in consumer products [10,11]. They are widespread and found anywhere on the planet, making exposure to EDCs ubiquitous for wildlife and human populations [10,11]. In addition, some EDCs have long half-lives, are highly resistant to metabolic degradation and can be stored for years in adipose tissue due to their lipophilic nature [for example, organochlorine pesticides, such as dichlorodiphenyltrichloroethane (DDT), dioxins and heavy metals] [12]. However, other EDCs that are rapidly degraded in the environment or the human body, or so widespread in their use like bisphenol A (BPA), can also have serious deleterious effects if exposure occurs during critical developmental periods [10].

The concept of EDCs was first proposed 20 years ago, when a number of observations concerning deleterious effects on reproductive development and gender differentiation focused on EDC interference with sex steroid hormones [13]. Indeed, many of these chemical products, such as DDT or other organochlorines, exhibit oestrogenic and/or antiandrogenic effects, and are able to interact during early embryonic development and/or reproduction (Table 1). A spectrum of disorders are related to EDC exposure and some of them are sexually dimorphic: cryptorchidism, hypospadias, oligospermia and testicular cancer *in situ* as well as prostate hyperplasia are seen in males; whereas precocious puberty (including premature thelarche and premature pubarche), sexual precocity and, more recently, ovulatory disorders (such as polycystic ovary syndrome, or PCOS) have been suggested to be linked to EDC exposure in females [10].

It is well known that oestrogens and other sex hormones regulate the functioning of tissues involved in reproduction. They also play a fundamental role in the physiology of behaviour, bone development and immunity. In fact, the ancestral oestrogen receptor (ER) was already present in invertebrates lacking

Table 1
Chemical compounds considered endocrine disruptors due to their oestrogenic and/or antiandrogenic effects and activation of peroxisome proliferator-activated receptors (PPARs).

	Molecules	Usual source of exposure
Oestrogen mimetics	Oestradiol, oestrone, oestriol	Natural synthesis (residual water)
	Ethinyl oestradiol	Contraception (residual water)
	Diethylstilbestrol (DES)	Sedative
	Tamoxifen	Breast cancer
	Coumestrol, genistein	Phytoestrogens
	Zearalenone	Mycotoxin
	Aldrin, dieldrin, endosulphan, chlordecone (Kepone)	Organochlorine insecticides
	Atrazine	Herbicide
	Polychlorinated biphenyls (PCBs), nonylphenols	Industrial fluids, detergents, solubilizers
	Bisphenol A	Plasticizer
	Furans	Byproducts of thermal degradation of food
Oestrogen mimetics & antiandrogenic effects	Methoxychlor	Fungicide, insecticide
	Dichlorodiphenyltrichloroethane (DDT) and metabolites	Insecticides
	TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin)	Waste incineration, wood combustion
PPAR activators	Bisphenol A	Plasticizer
	Phthalates	Plasticizers
	Tributyltin	Biocide (antifouling paint)
	Perfluorinated acids (PFOA, PFOS)	Surfactants
	Parabens	Antimicrobial preservatives (cosmetics)

PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulphonic acid.