Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

Sex-specific metabolic alterations induced by environmental pollutants

Brigitte Le Magueresse-Battistoni, Hubert Vidal and Danielle Naville

Abstract

Diabetes and obesity are the biggest public health challenge and the current prevalence of these chronic diseases has reached epidemic proportions worldwide. Apart from genetic alterations and lifestyle, exposure to environmental chemicals has emerged as a new cause of metabolic diseases. Notably, several compounds that mimic or oppose hormone activity defined as endocrine disruptors (EDs), may exert metabolic disturbances through interfering with the regulatory roles of the sex steroids (among other hormones) in energy homeostasis. However, most studies to date have investigated the metabolic impact of EDs on males and there is a lack of information regarding the metabolic impact of endocrine disruptors in females. There is as well a paucity of data for both sexes related to the metabolic impact resulting from the exposure to a mixture of EDs which is a more realistic scenario than the exposure to chemicals individually. Hopefully, conducting studies on both sexes in situations of multi-exposure to chemicals will help at better understanding the sex-biased mechanisms linked to endocrine disruption that could be helpful to improve and personalize treatments of diseases for which obesity is a risk factor, such as the metabolic syndrome and the hormono-dependent cancers.

Addresses

Univ-Lyon, CarMeN Laboratory, INSERM U1060, INRA U1397, Université Claude Bernard Lyon1, INSA Lyon, Charles Mérieux Medical School, F-69600 Oullins, France

Corresponding author: Le Magueresse-Battistoni, Brigitte (brigitte.lemagueresse@inserm.fr)

Current Opinion in Toxicology 2018, **8**:1–7

This review comes from a themed issue on **Mechanistic Toxicology: Metabolic Disruption**

Available online 16 November 2017

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2017.11.007

Keywords

Endocrine disruptors, Energy homeostasis, Sex-dimorphism, Insulin signaling, Glucose tolerance, Cholesterol metabolism.

1. Introduction

Diabetes and obesity are the biggest public health challenge and the current prevalence of these chronic diseases has reached epidemic proportions worldwide. By 2030, it is predicted that the number of overweight people will reach 3.3 billion while diabetes will affect more than 400 million people worldwide becoming a leading cause of death [1]. Apart from genetic alterations and lifestyle, exposure to environmental chemicals has emerged as a new cause of metabolic diseases. Notably, several compounds display estrogeno-mimetic activities and models of estrogen deficiency/excess in both humans and rodents, both in males and females have well illustrated the importance of estrogens in regulating energy homeostasis and insulin sensitivity when estrogens stay within tight physiological concentrations. Indeed, energy homeostasis is largely dependent on sex-specific mechanisms regulating eating behavior, energy expenditure, fat distribution, insulin sensitivity and glucose tolerance [2]. Accordingly, it was anticipated that compounds with estrogenic, anti-estrogenic or anti-androgenic activities will act as metabolic disruptors and that the adverse effects may be sex-specific.

In this commentary, we intend to highlight that environmental pollutants and among them endocrine disruptors exert metabolic disturbances through interfering with the signaling of sexual hormones, with both common and sex-biased specific effects. A focus is made on the use of a mixture of endocrine disruptors which corresponds to a more realistic scenario than the use of individual chemicals.

2. Historical context

A thousand chemicals have been identified as endocrine disruptors including persistent organic molecules but also pharmaceuticals, phytoestrogens, mycotoxins [3–5]. These products which have invaded the different compartments of the environment (biota, air, water, land and aquatic sediments), accumulate and concentrate in organisms higher up the food chain (bioaccumulation). As a consequence fatty products contain a high level of persistent and lipophilic chemicals (e.g., dioxins and polychlorobiphenyls, PCBs). Food may also be contaminated by short-lived molecules such as phthalates and bisphenols migrating from food packaging and containers. Eventually, exposure to various chemicals may occur by inhalation and dermal contact as well as by breastfeeding and by hand-to-mouth behavior in children.

The modes of action of the endocrine disruptors are not fully characterized because they are dependent on the dose of the chemicals, the simultaneous presence of other chemicals defined as the cocktail effect (detailed

later in the Commentary), the timing of exposure and the sex of the exposed individuals [6]. For example, the set of genes activated in the liver of bisphenol A (BPA)-exposed male rats depends on the dose of BPA [7]. One chemical may interact with multiple nuclear receptors (e.g., steroid receptors, xenobiotic/endobiotic receptors, the aryl hydrocarbon receptor) [6,8] and/or interfere with the signaling of different hormones such as estrogens, androgens and thyroid hormones (e.g., BPA, dioxins, phthalates and PCBs) [9]. In addition, and contrasting with the toxicology principles, the adverse effect does not obligatory occur immediately post exposure. Its occurrence is highly dependent on the timing of exposure with windows of high vulnerability coinciding with the period of differentiation of the targeted organ. For example, the fetal and perinatal periods during which food behavior, energy expenditure and differentiation of the adipose tissue are occurring constitute highly vulnerable periods, as well as puberty [3–5]. Finally, epigenetic mechanisms have been demonstrated to support adverse effects observed later in life (Developmental Origin of Human adult Diseases or DOHaD hypothesis) [10] and in non-exposed generations born from grandparents exposed during the fetal or lactation periods (transgenerational effects) [10,11].

Because it has long been considered that physiological systems were similar in males and females, few experimental studies have investigated both sexes preferring males mostly because of the suspected variability due to estrous cyclicality in females. Interestingly, the discovery that chemicals were inducing developmental and reproductive disorders by interfering with any aspect of hormone action (which is the accepted definition of the endocrine disruptors, [12]) had probably opened increasing interest in studying the two sexes but also the fetal and pubertal periods as well as the menopausal period. Indeed, these periods are marked by tremendous hormonal changes governing most of the physiological functions (e.g., behavior, reproduction, development, growth and energy homeostasis). As a matter of fact, first adverse effects of these chemicals were described in the field of reproduction consistent with a high number of these chemicals interfering with the signaling of estrogens and androgens. Historically, three chemicals, which are the drug diethylstilbestrol (DES), the pesticide dichlorodiphenyltrichloroethane (DDT) and the antifouling paint tributyltin (TBT) have been instrumental in the understanding of the modes of actions of the endocrine disruptors [8,13,14].

3. Energy homeostasis is a physiological function with strong sex-dimorphic traits and thus at high risk of alteration by endocrine disruptors

Energy homeostasis comprises regulation of food behavior and efficiency, and of glycaemia at physiological levels to meet energy demands. Regulation of glycaemia involves insulin secretion by the pancreas and insulin action on liver, muscle and adipose tissues. Dysregulation as a result of pancreatic failure in insulin production or inappropriate response to insulin (i.e., insulin resistance) induces a spectrum of metabolic disturbances such as obesity, glucose intolerance, dyslipidemia, hyperinsulinaemia, low-grade inflammation leading among others to the development of diabetes or cardio-vascular diseases. An obesogen chemical will be defined as a chemical interfering with food intake and energy expenditure, energy efficiency or adipocyte hyperplasia (proliferation) and/or hypertrophy (differentiation) while a metabolic disruptor chemical (diabetogen) will interfere with insulin secretion, insulin action or both [15]. However, the distinction is not that obvious as obesity is a risk factor for diabetes.

Sexual dimorphism of the process is mostly driven by the genetic sex, the programming effect of testosterone in males during the perinatal period, and the role of sex hormones at puberty [2]. For example, experimental exposure of females to testosterone during the perinatal period (which normally occurs in males but not in females) induces male food behavior via the androgen receptors (ARs) and leptin-resistance through activation of the estrogen receptors (ERs), both concurring to obesity in adulthood [16]. Developmental androgen excess disrupts as well energy homeostasis in adult male mice predisposing them to obesity [16]. The perinatal period is also marked by the programming of mesenchymal stem cells toward either the adipocyte or the bone lineage involving among others concurrent activation of ERs and peroxisome proliferator-activated receptors (PPARs) [17], and many xenobiotics promote adipogenesis through these receptors including the previously mentioned historical molecules (DES, TBT and DDT) [4,6,11].

Fat distribution is a highly sex-dimorphic trait more evidenced in adulthood. Although females have more subcutaneous adipose mass than males and males more muscle mass than women, fat subcutaneous distribution is not detrimental as compared to males which accumulate visceral fat upon body weight gain predisposing them to diabetes and cardiovascular diseases [2]. Importantly, excess of estrogens such as during the estrous periods, during gestation and through pill consuming, results in insulin resistance favoring weight gain while estrogen deficiency such as during the menopausal transition also favors weight gain, accumulation of visceral fat and development of type 2 diabetes. Males and females also differ in the utilization of carbohydrates and lipids as fuel sources [18–20]. It indicates that while estrogens protect females from metabolic disorders in a physiological dose-range, exposure at a wrong period of time or at inappropriate levels can elicit adverse metabolic consequences like exposure to androgenic chemicals. In males,