General and Comparative Endocrinology 170 (2011) 416–423

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

Review

Perspectives on endocrine disruptor effects on metabolic sensors

B. Migliarini [a], C.C. Piccinetti [a], A. Martella [a,1], F. Maradonna [a], G. Gioacchini [a], O. Carnevali [a,b,*]

[a] Dipartimento di Scienze del Mare, Università Politecnica delle Marche, Via Brecce Bianche, 60131 Ancona, Italy
[b] Istituto Nazionale Biostrutture e Biosistemi, viale Medaglie d'Oro 305, 00136 Roma, Italy

ARTICLE INFO

Article history:
Received 28 July 2010
Revised 17 November 2010
Accepted 24 November 2010
Available online 3 December 2010

Keywords:
EDs
Body weight
Food intake
Lipid metabolism

ABSTRACT

Endocrine disrupting (EDs) chemicals can increase or block the metabolism of endogenous peptidergic or steroid hormones by activating or antagonizing nuclear receptors in the hypothalamus, besides adipose tissue, liver and gonads.

Toxicological and epidemiological studies have suggested the involvement of different EDs in an increasing number of metabolic disorders such as obesity and diabetes.

The aim of this review is to summarize the literature from experimental animal studies demonstrating the impairment of body weight raised by the deregulation of peptidergic signals as well as by the activation of key metabolic molecular targets.

Regarding the modification of gene transcription levels induced by EDs, new data on DEHP effect on food intake and lipid metabolism in the experimental model zebrafish (*Danio rerio*) have also been included in this review providing evidences about the dangerousness of DEHP low doses.

1. Introduction

Energy homeostasis derives from the balance between the amount of consumed food and energy expenditure. It depends on the recognition of energy stores present in adipose tissue in order to keep these stores adequate to the period of life of the organism.

This regulation occurs *via* the interaction of peripheral hormones with peptidergic neurons organized in circuitries, in which neuropeptides interact with each other and with monoaminergic and other types of neurotransmitters and are known to be sensitive to signals from the periphery, thus allowing the hypothalamus to sense the status of body energy stores and regulate food intake and energy expenditure [39,91].

The brain, particularly the hypothalamus, produces key factors that either stimulate (orexigenic) or inhibit (anorexigenic) food intake [100]. It is notable that many of the mediators involved in the neuronal control of appetite behaviour are known to be implicated in the regulation of peripheral energy metabolism and vice versa [46].

Glucose is the only energy source for the brain except for long lasting starvation periods, when ketones belonging from the liver cover this lack. Nevertheless the hugest stock of metabolic fuel comes from adipose tissue where triacylglycerol are synthesized and collected. The adipose tissue works as an endocrine organ that secretes numerous hormones, growth factors, enzymes, cytokines, and complement factors that participate in the body's feedback system regulating appetite and food intake.

This complex cross talk among molecules belonging from different organs can maintain the energy balance as long as all the components are well-orchestrated. If a link in this connection is disrupted by genetic, nutritional, environmental or pathological factors the entire system may be deranged resulting in metabolic or eating disorders such as obesity, diabetes, anorexia nervosa [9,61,18].

As the onset of these diseases is a huge public concern, many studies are focusing on this item. In this review we intend to summarize those regarding environmental endocrine disruptors effect on energy balance maintenance.

2. EDs impair body weight

Many substances, both natural and synthetic, are known to interfere with endocrine signaling pathways both in human and wildlife

Abbreviations: EDs, endocrine disruptors; DEHP, dietylexilphthalate; DDT, dichloro-diphenyl-trichloroethane; DES, diethylstilbestrol; BPA, bisphenol A; PCBs, polychlorinated biphenyls; TCDD, tetrachlorodibenzo-*p*-dioxin; HxCDD, hexachlorodibenzo-*p*-dioxin; PEPCK, phosphoenolpyruvate carboxykinase; DEHP, diethyl-hexyl-phthalate; ER, estrogen receptor; LPT, leptin; GHR, ghrelin; NPY, neuropeptide Y; POMC, propiomelanocortin; AgRP, agouti related protein; ORX, orexin; ECS, endocannabinoid system; AEA, anandamide; 2-AG, 2-acyl-glycerol; AMPK, 5′-AMP-activated protein kinase; NP, nonylphenol; Cb1, cannabinoid receptor 1; Cb2, cannabinoid receptor 2; DiBP, diisobutyl phthalate; DBP, dibutylphthalate; PPARs, peroxisome proliferator activated receptors; GD, days of gestation; RXR, retinoic acid receptor; SREBP, sterol regulatory binding protein; TBT, tributyl tin chloride; SREBP, sterol regulatory binding protein; POP, persistent organic pollutants; PBDE, polybrominated diphenylethers.

* Corresponding author at: Dipartimento di Scienze del Mare, Università Politecnica delle Marche, Via Brecce Bianche 60131 Ancona, Italy. Fax: +39 071 2204650.

E-mail address: o.carnevali@univpm.it (O. Carnevali).

[1] Present address: Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, via Campi Flegrei 34, Comprensorio Olivetti, 80078 Pozzuoli, Naples, Italy.

0016-6480/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygcen.2010.11.025

and are commonly named endocrine disruptors (EDs) [93,99,10,92,11,69,33]. These chemicals are widespread in the environment and include synthetic organic compounds such as pesticides (e.g. dichloro-diphenyl-trichloroethane, DDT), pharmaceutical drugs (e.g. diethylstilbestrol, DES), chemicals used in the synthesis of plastics and resins (bisphenol A, BPA), phthalates, dioxins, polychlorinated biphenyls (PCBs), and natural phytoestrogens (genistein), etc. In different animal experimental models, this interaction has been documented to generate adverse health outcomes by impairing fundamental physiological processes [71,89,40,41].

Although the scientific community initially focused on EDs impairment of reproduction and development, recently, the interference of EDs with receptors regulating metabolism has been proposed especially in relation with the etiology of metabolic diseases such as obesity and diabetes [67,68,13].

In particular, the harmful action of EDs on normal adipocyte development, homeostatic control of adipogenesis, early energy balance and in turn on body weight has been demonstrated [31].

The dioxin tetrachlorodibenzo-*p*-dioxin (TCDD), a widespread chemical resistant to biodegradation [12], has been found to be present in the human body for long periods of time [84].

As well as being a developmental and reproductive toxicant [15], TCDD has been found to cause a dose-dependent decrease in body weight, food intake, resting and total oxygen consumption, resulting in the so-called wasting syndrome. Rats treated with a lethal dose (50 μg/kg) lost weight continuously after treatment and generally died. The similar dose and time dependencies for reduction of food intake and weight suggest that hypophagia is the major factor responsible for weight loss in TCDD-treated rats. When allowed to feed *ad libitum* immediately after treatment, these animals exhibited relative hyperphagia and weight gain, demonstrating that TCDD did not impair their capacity to feed once the exposure is stopped [87]. More recently, high doses of TCDD and the hexachlorodibenzo-*p*-dioxin (HxCDD) (3.2 and 80 mg/kg, respectively) in rats were found to induce a slight increase in body weight with respect to controls, while low doses of these compounds (0.05 and 1.25 mg/kg, respectively) induced a significant weight loss. The reduction in body weight occurred *via* the inhibition of IGF-I circulating levels and of phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression [19].

Many reports have suggested that, together with dioxin, PCB concentrations in the bodies of pregnant women are also negatively correlated to the birth weight of the women's infants [22,75]. In particular, Tajimi and colleagues [94] recently analyzed PCDD/F and Co-PCB concentrations in breast milk samples collected from 240 mothers and related the presence of these pollutants with the birth weight of their infants, finding that birth weight was negatively correlated with the concentration of many of the PCDD/F and Co-PCB congeners.

Many studies have shown that exposure to numerous EDs during critical periods of differentiation, at low environmentally-relevant doses, can alter developmental programming and lead to obesity [64–66,29].

Among these contaminants, genistein, which belongs to the phytoestrogen family and is one of most abundant phytoestrogens in the human diet, is able to induce body weight gain in neonatal exposed rats [66]. Additional information about genistein impairment of energy homeostasis was supplied by Penza et al. [77] who hypothesized that at pharmacologically high doses genistein inhibits adipose deposition but, at low doses similar to those found in Western and Eastern diets, in soy milk, or in food supplements containing soy, it induced adipose tissue deposition especially in males. Surprisingly, genistein was not found to significantly affect food consumption.

Of great interest for its prevalence in our environment is the plasticizer BPA, chemical widely found in human serum because of its common use as a plasticizer in the production of polycarbonate and epoxy resins. Both perinatal and post-natal exposures have been analyzed and a significant impact on body weight determination has been stated [70]. Rubin and collaborators [83] exposed rat dams to 0, 1 or 1, 2 mg BPA/kg BW/day in drinking water and the all offspring (males and females) showed an increase in body weight. In a further study, BPA given to rat females during pregnancy period was also found to grow rat body weight of the litter in the adulthood [95]. With regard to post-natal BPA exposure, male rat pups injected at birth day for 4 days with 50 mg BPA/kg BW/day exhibited heavier body weight at post-natal day 68 respect to control [76] as well as female mice treated from day 1 to day 5 post birth with 10 mg BPA/kg BW/day at 18 months of age showed a 11% higher body weight respect to controls [65].

With a similar behaviour to BPA, the potent synthetic estrogen DES, widely prescribed to woman until 1971 for the management of the miscarriage risk, resulted in body weight depression if given to neonatal female mice during the period of adipocyte differentiation at high doses (1 mg/kg). Conversely, after 2 months of age a persistent enlargement of abdominal fat pads was observed in the same animals. Instead, DES exposed males did not became obese but rather showed a dose-dependent decrease in overall body weight [65,66].

Among plasticizers, the phthalate di-ethyl-hexyl-phthalate (DEHP) worth particular attention for its wide presence in the soil and water that has been considered a priority environmental concern by North American and Europe governments. When suspended in the water, its half life is around 2–5 weeks while, in the sediments, captured by particulate matter, has been estimated to be over 100 years due to unavailability for biodegradation.

DEHP was found to inhibit the growth of guppy (*Poecilia reticulata*) in terms of body weight and body length. DEHP 10 μg/L applied continuously for 91 days as early as 14 days after the start of exposure induced significantly reduced body length as compared with control fish. The effect was even more pronounced for body weight which was diminished of 70%. The reduction in growth was still significant at 91 days of DEHP treatment [106].

A notable reduction in body weight was also reported in a study conducted on Wistar rats fed with standard diet supplemented with 2% DEHP (W/W) for 21 days. Surprisingly, this decrease was not supported by any changes in food intake levels [55].

Genistein, BPA and DEHP are considered estrogenic compounds and the attention on these category of pollutants has to be maintained very high as long as estrogens, are to date known to be crucial for energy homeostasis maintenance [49,80,81].

The depletion of the estrogen receptor ERα in ventromedial nucleus of the hypothalamus was found to bring to body weight increase, hyperphagia and hyperglycemia in female mice [62]. It is notable that this phenotype persisted despite normal ER levels elsewhere in the brain. Although an increase in food intake preceded weight gain, Musatov and collaborators suggested that a leading factor of obesity in their study is likely a decline in energy expenditure [62].

3. EDs derange hypothalamic signals

What is of great interest is the comprehension of the molecular mechanisms that bring to this body weight deregulation and, in general, to energy balance impairment.

Important progresses in the understanding of how body weight set point is controlled has been made by the characterization of hypothalamic circuitries which regulate energy intake and expenditure, whereby neuropeptides play an important role [85,86].