Endocrine disrupting chemicals alter neuronal circuits controlling reproduction and appetite

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Abstract :

Exposure to endocrine disrupting chemicals during critical periods of development can result in detrimental long-term health consequences. The hypothalamus is extremely sensitive to endocrine disrupting chemicals, which could participate to the increase in metabolic and reproduction related diseases. We propose the concept according to which exposure to low levels of endocrine disrupting chemicals induces developmental
and transgenerational alterations of sexual maturation and energy balance through reprograming of the hypothalamus.

1. Introduction

Obesity prevalence has been escalating worldwide. However, it appears that the classical obesity risk factors, increased food intake, sedentary lifestyle and genetics are probably not sufficient to explain the rapid increase in obesity incidence [1]. Of note, overweight is more common in men, but severe obesity is more frequent in women, highlighting notable sex differences that are not always sufficiently accounted for.

Similarly, over the last few decades, female reproductive health disorders have steadily increased in frequency. Data from both Europe and North America suggest a secular trend toward earlier onset of puberty [2] concomitant with an increase in idiopathic central precocious puberty in girls [3]. The incidence of polycystic ovarian syndrome (PCOS) and endometriosis has consistently been increasing [4], and worrying statistics show significantly reduced female fertility [5]. Along the same line, markedly increased incidences in testicular cancers together with decreased sperm quality in recent decades indicate that environmental factors might be responsible [6].

Although these are all multifactorial disorders involving genetic and life-style factors, a growing body of evidence indicates the contribution of exposure to endocrine disrupting chemicals (EDCs). Human populations are exposed to an increasingly large array of synthetic chemicals [7]. Among 85,000 chemicals in use, 1000 have been identified as having the ability to disrupt normal endocrine function. EDCs impact fetal development and increase the risk of diseases such as abnormal sexual development, adult reproductive failure, obesity and metabolic syndrome [7] (Fig. 1). Beside the gonads, pancreas and adipocytes, it appears that the hypothalamic circuits controlling puberty, reproduction and energy balance are also sensitive to endocrine disruption. However, the current regulatory procedures do not provide efficient screening to identify EDCs and limit their use.

2. Hypothalamic control of puberty and reproduction : a target for EDCs

Puberty begins with the reactivation of gonadotropin releasing hormone (GnRH) neurons in the hypothalamus after a period of postnatal quiescence. Pubertal activation of the GnRH pulse generator involves a shift from inhibitory to excitatory inputs onto GnRH neurons which will eventually lead to the ability to reproduce. While glutamate and GABA are key modulators of GnRH neuron activity, studies have identified additional critical factors, including the neuropeptide kisspeptin, its receptor GPR54, neurokinin B, and makorin ring protein 3 (MKRN3) [8]. This extrinsic pulse generator appears particularly sensitive to sex steroid, and energy balancerelated hormones [8]. Recent data indicate that the transcriptional and epigenetic control of the pulse generator is also very sensitive to both estrogenic and anti-androgenic EDCs [9–11], particularly during gestation and lactation periods, affecting GnRH activity, puberty and long-term fertility [11]. The potential EDC targets within this pulse generator include potent GnRH inhibitors such as GABA and MKRN3, or activators such as oxytocin and kisspeptin [9–11]. Additionally, EDCs can have transgenerational effects on the hypothalamic control of puberty and reproduction. Ancestral exposure to a mixture of 13 EDCs delayed puberty and the maturation of GnRH secretion in the third generation

of rats (F3), affecting hypothalamic Kiss1 expression. F3 females displayed a disbalanced histone configuration at the Kiss1 promoter with higher expression of the repressive H3K27me3 and lower H3K4me3–a histone modification found in promoter regions of activated genes– suggesting that the delay in pubertal timing was mediated by an alteration of the epigenetic switch of polycomb Group and trithorax complexes known to regulate KISS1 transcriptional activation at puberty [12].

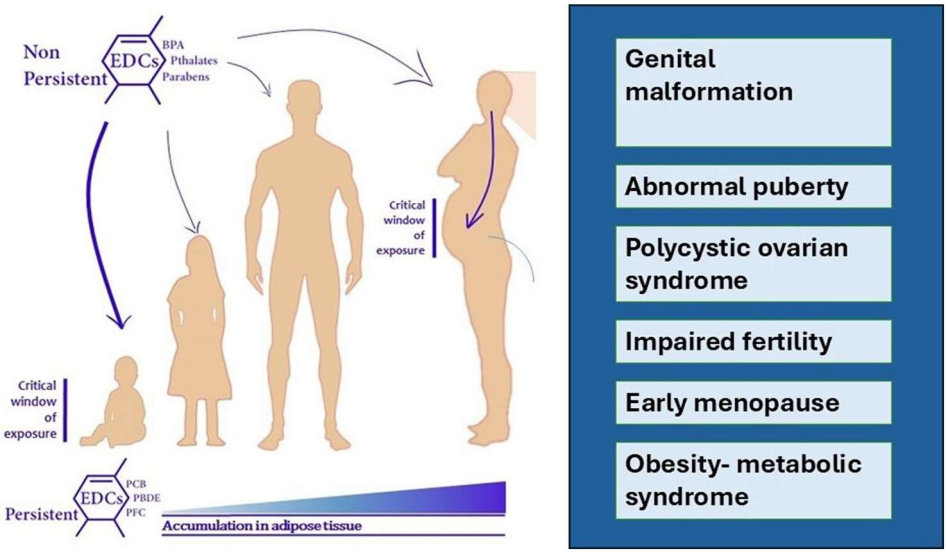

Fig. 1. The hypothalamus is sensitive to ubiquitous persistent and non-persistent endocrine-disrupting chemicals (EDCs) particularly during critical windows of development. Ultimately, alterations caused by EDCs could lead to abnormal sexual development, abnormal puberty, infertility and obesity or metabolic syndrome. BPA: bisphenol A; PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls; PCOS: polycystic ovary syndrome; PFCs: perfluorinated compounds.

3. Hypothalamic control of energy balance : a target for EDCs

The hypothalamus is an essential component of the neuroendocrine and pre-autonomic circuits controlling energy homeostasis [13]. Its control of energy balance involves a series of interconnected neural networks with the arcuate nucleus being the primary site for integration of hormonal (leptin, ghrelin, insulin) and environmental cues. Pro-opiomelanocortin (POMC) and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons compose the melanocortin system within the hypothalamus [13]. Those neurons are generated during embryonic life and acquire their cell fate under transcriptional and epigenetic control [13]. During the postnatal period, they establish projections toward the paraventricular nucleus which will be crucial for the control of energy balance later in life [13]. Those neuronal populations appear to be extremely sensitive to environmental cues early in life with profound metabolic consequences later in life [13]. Studies have shown that, in addition to affect insulin production and adipogenesis, developmental exposure to EDCs increases food intake and affect hypothalamic neuronal circuits controlling energy balance.

In vitro studies indicate that bisphenol A (BPA) affects NPY and POMC mRNA expression through oxidative stress and neuroinflammatory mechanisms [14,15]. Following developmental exposure to BPA, mice were resistant to leptin-induced suppression of food intake and hypothalamic POMC upregulation. Additionally, mice showed a reduced density of POMC projections into the paraventricular nucleus [16]. Tributyltin, which also affects food intake in mice leads to altered electrical activity of hypothalamic neurons expressing leptin receptor [17,18].

4. Conclusion

In addition to lifestyle, early environmental factors among which Endocrine disrupting chemicals (EDCs) play a role in the current impairment of reproductive and metabolic health. Laboratory studies indicate that the hypothalamic circuits controlling energy balance and reproduction are very sensitive to endocrine disruption. Recent advances in high throughput approaches have helped to identify unsuspected mechanistic pathways of EDCs in the hypothalamus involving transcriptional and epigenetic modifications. In the future spatial transcriptomics/proteomics will help elucidate which cell types regulating reproduction are most sensitive to epigenetic and transcriptomic modifications induced by EDCs.
Multiple recent studies have identified transgenerational transmission of reproductive and metabolic alterations in rodents. These results indicate that transgenerational disruption induced by EDCs happen through germ cell alterations. The mechanisms by which EDCs affect germline programming and induce somatic alterations needs to be further explored.

Disclosure of interest

The authors declare that they have no competing interest.

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