

Title

Transgenerational alterations of energy balance caused by a mixture of endocrine disrupting chemicals in rats

Abstract

The prevalence of obesity has been rising worldwide for several decades. Obesity is associated with multiple risk factors, such as a lack of physical exercises, unbalanced diet, but also genetic or environmental factors such as developmental exposure to endocrine disrupting chemicals (EDC). Our recent data have indicated that transgenerational exposure to a mixture of EDC disrupted the hypothalamic control of puberty and reproduction in F3 female rats. The aim of the current study is to characterize the effects of a transgenerational exposure to such mixture of EDC on energy balance in male rats. Wistar dams (F0) were orally exposed to a mixture of 13 anti-androgenic or estrogenic EDC at environmentally relevant doses starting 2 weeks before mating, during gestation and until lactation.

F3 males ancestrally exposed to EDC showed a significantly higher body weight than the control group during the adulthood. This increased weight gain at 3 months (Mean body weight \pm SD: CTRL: 454.7 \pm 19.51 g; EDC: 483.6 \pm 26.1 g; T-test p-value = 0.0027) was associated with a significant increase in food intake (Mean food intake \pm SD: CTRL: 32.5 \pm 1.3 g; EDC: 36.9 \pm 1.1 g; Mann-Whitney test p-value <0.0001). Consistently, the weight of gonadic white adipose tissue (WATg) (Mean WATg weight \pm SD: CTRL: 6.85 \pm 1.2 g; EDC: 9.16 \pm 2.8 g; T-test p-value = 0.0133) and average adipocyte size (Mean adipocyte size \pm SD: CTRL: 3051 \pm 369 μm^2 ; EDC: 4507 \pm 341 μm^2 ; T-test p-value <0.0001) were increased after the transgenerational EDC exposure. From a mechanistic perspective, the study of the hypothalamic pathway controlling the energy balance (melanocortin system) showed that ancestral EDC exposure altered the neuronal network controlling satiety. Indeed, the density of POMC (α -MSH) neuron axonal fibers was reduced in the paraventricular nucleus of the hypothalamus of EDC exposed F3 males (Mean α -MSH fiber density \pm SD: CTRL: 0.032 \pm 0.002; EDC: 0.028 \pm 0.002; T-test p-value = 0.0249).

In conclusion, transgenerational exposure to a mixture of EDC leads to an obesogen-like phenotype in F3 males, coupled with an alteration of the hypothalamic melanocortin system controlling the energy balance.

Co-authors

Glachet Chloé¹, Franssen Delphine^{1,2}, Jacquinet Charlotte¹, Terwagne Quentin¹, Sevrin Elena¹, Pinson Anneline¹, Parent Anne-Simone^{1,3}

¹ GIGA Neurosciences, Neuroendocrinology Unit, University of Liège, Belgium

² Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

³ Department of Pediatrics, University Hospital Liège, Belgium