Title

Transgenerational alterations of energy balance and hypothalamic melanocortin system caused by a mixture of endocrine disrupting chemicals in rats

Abstract (with HFD)

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. Third generation males (F3) were then exposed to a high fat diet (HFD, 45% fat) between 3 and 6 months of age (n= 14 for standard diet controls (CNN) and EDC (ENN), n= 13 for HFD controls (CHFD) and EDC (EHFD)).

F3 males ancestrally exposed to EDC showed a significantly higher body weight than the control group during the adulthood. This increased weight gain (Mean body weight ± SD: CNN: 570.2 ± 24.1 g; CHFD: 593.5 ± 29.3 g; ENN: 628.5 ± 38.1 g; EHFD: 630.5 ± 48.1 g) was associated with a significant increase in food intake (CNN: 34.7 ± 0.8 g; CHFD: 21.9 ± 1.1 g; ENN: 36.7 ± 3.02 g; EHFD: 25.8 ± 4.4 g). Consistently, the ratio of gonadic gonadic white adipose tissue weight over body weight (WATg) (Mean WATg weight ± SD: CNN: 0.011 ± 0.001 g; CHFD: 0.013 ± 0.002 g; ENN: 0.013 ± 0.003 g; EHFD: 0.014 ± 0,002 g) and average adipocyte size (Mean adipocyte size ± SD: CNN: 3051 ± 369 μm^2; CHFD: 4020 ± 627 μm^2; ENN: 4507 ± 341 μm^2; EHFD: 4304 ± 1127 μm^2) was increased after the transgenerational EDC exposure. From a mechanistic perspective, the study of the hypothalamic pathway controlling the energy balance (melanocortin system) showed a consistent decrease of the axonal fiber density of POMC neurons (α-MSH) controlling satiety, going from the arcuate nucleus to the paraventricular nucleus of the hypothalamus of F3 males before HFD exposure (Mean α-MSH fiber density ± SD: CTRL: 0.032 ± 0.002; EDC: 0.028 ± 0.002).

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 energy balance.

Co-authors

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