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

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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 were orally exposed to a mixture of 13 anti-androgenic or estrogenic EDC at environmentally relevant doses 2 weeks before mating, during gestation and 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 at 3 months of age, before exposure and throughout the HFD treatment period. 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 increase in the ratio of 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 µm² ; CHFD : 4020 ± 627 µm² ; ENN : 4507 ± 341 µm² ; EHFD : 4304 ± 1127 µm²) was affected by EDC and HFD exposure. F3 males ancestrally exposed to EDC and exposed to HFD showed a significant decrease in testicular weight (Mean testicular weight/ body weight ± SD: CNN : 0,0033 ± 0,0004 g ; CHFD : 0,0033 ± 0,001 g ; ENN : 0,0027 ± 0,0005 g ; EHFD : 0,0028 ± 0,0003 g) and FSH plasma levels (Mean FSH levels ± SD: CNN : 3,42 ± 0,35 ng/ml ; CHFD : 3,73 ± 0,97 ng/ml ; ENN : 3,21 ± 0,54 ng/ml ; EHFD : 3,10 ± 0,28 ng/ml) although testosterone, LH levels and sperm count were not affected.

In conclusion, transgenerational exposure to a mixture of EDC worsened the obese phenotype of F3 male rats induced by HFD. We hypothesize that such effects could be explained by a disruption of hypothalamic circuits controlling food intake.