Perinatal exposure to n-Butylparaben increases body weight in female offspring

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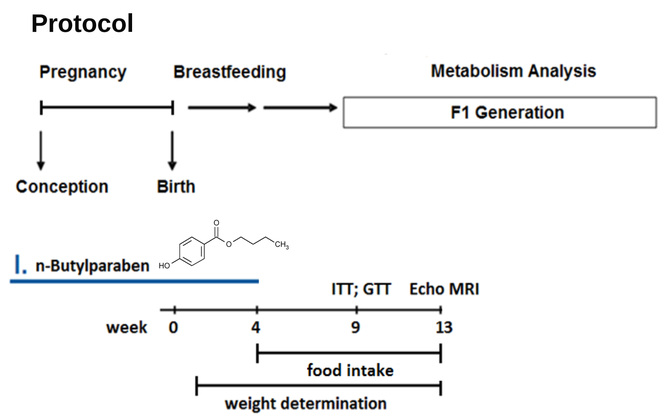
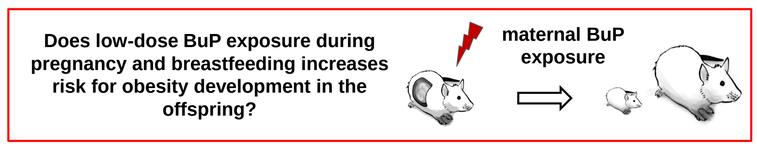
Introduction

Parabens are ester of 4-hydroxy-benzoic acid and widely used preservatives in a variety of consumer products such as food, cosmetics and pharmaceuticals. The risk of low-dose exposure to parabens for human health has been discussed controversially in recent years. Previous data from animal studies suggest that parabens like n-Butylparaben (BuP) may act as endocrine disruptors and affect the reproductive system or adipocyte differentiation. This effect is most tremendous in the early prenatal period when priming effects find a highly vulnerable time window.

The aim of the present study was to investigate the effect of maternal exposure to BuP on weight development and obesity risk in the offspring using a transgenerational mouse model.

Methods





Perinatal n-Butyl paraben exposure and offspring monitoring

BALB/c mice were exposed to BuP via subcutaneous injection to 140 µg/kg/week (correlates to the tolerable weekly intake, TWI) during pregnancy and breastfeeding. To investigate the effect of maternal BuP exposure to the offspring weight development we measured body weight for 12 weeks and determined body composition with EchoMRI technology. Furthermore we quantified food intake, analysed insulin and glucose metabolism and measured serum concentration of several adipocytokines with commercial ELISA. We analysed the expression of genes of interest with Real Time Quantitative PCR (qPCR).

Results

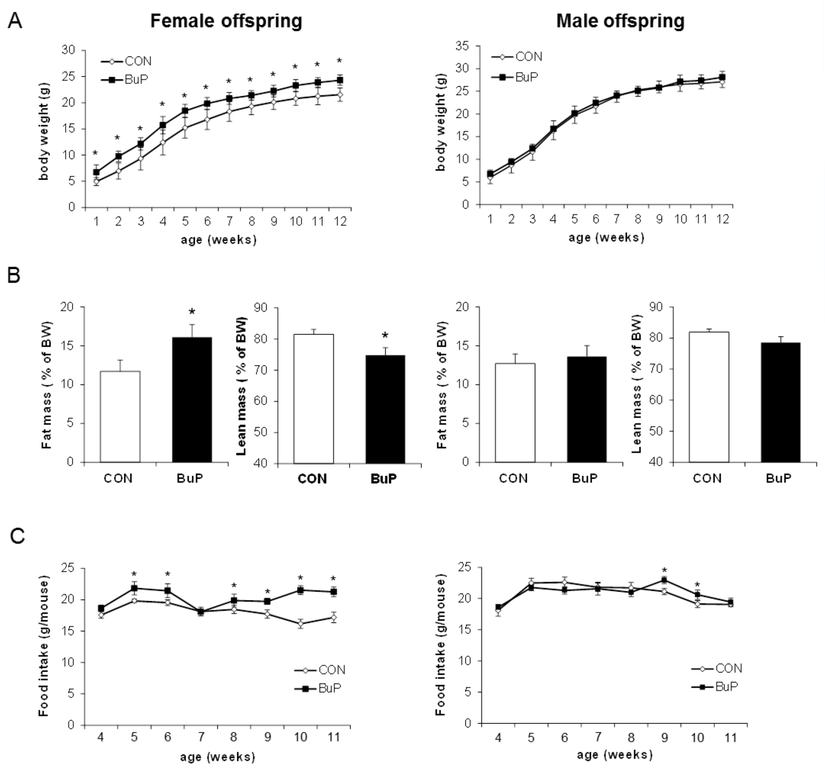


Fig. 1. Maternal exposure to n-Butylparaben (BuP) during pregnancy and breastfeeding increases obesity risk in female offspring.
Female offspring from Balb/c dams exposed during pregnancy and breastfeeding (Exposure Protocol) had a significant higher body weight over the entire measurement period (A) The elevated body weight became manifest shortly after birth and was linked to a significant higher fat and lower lean mass quantified by EchoMRI technology (B). Furthermore we were able to detect a higher food intake in female offspring (C).These results could not be determined in male offspring.
Data are expressed as mean ± SEM, n ≥ 8 animals per group;
*p < 0.05, one-way ANOVA (body weight) and t-test (remaining data).

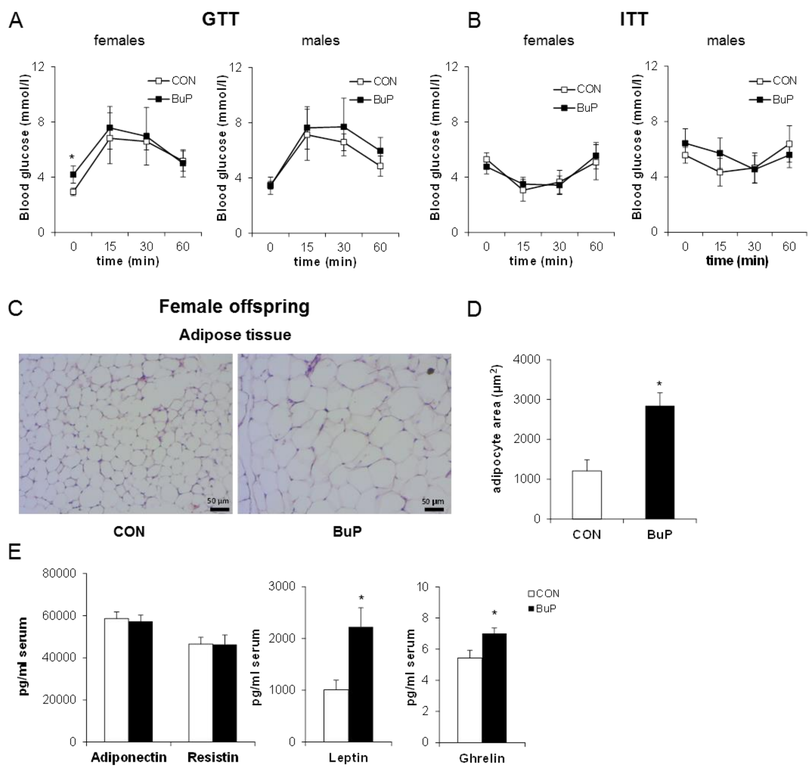


Fig. 2. Perinatal exposure to BuP increases adipocyte area, blood glucose and serum levels of leptin and ghrelin in female offspring.
The analysis of insulin and glucose metabolism with Insulin Tolerance and Glucose Tolerance Test displayed higher blood glucose levels in female offspring but no effects on insulin and glucose metabolism in female (A) and male offspring (B). Examination of adipocyte area with HE stained fat slices of female adipose tissue illustrated increased adipocyte area in female offspring (C-D) of BuP exposed dams in comparison to control group. Serum concentration of adiponectin and resistin remained unaffected but higher leptin and ghrelin levels were detectable (E).
Data are expressed as mean ± SEM, n ≥ 6 animals per group;
*p < 0.05 and t-test.

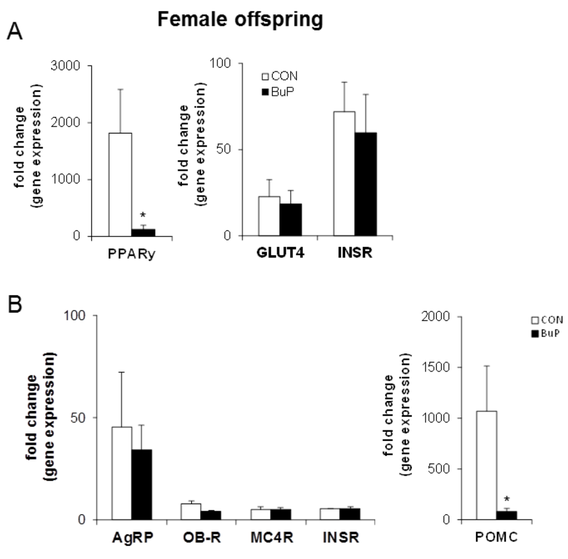


Fig. 3: Decreased expression of peroxisome proliferator-activated receptor gamma in adipose tissue and pro-opiomelanocortin (POMC) of hypothalamic neurons in female offspring in comparison to control group.
We were able to show a lower expression of peroxisome proliferator-activated receptor gamma in adipose tissue (A) with Real Time Quantitative PCR (qPCR). The expression of Glucose transporter type 4 (GLUT-4) and Insulin receptor (INSR) in adipose tissue remained unaffected (A). Furthermore a BuP exposure had no influence to expression of Agouti-related protein (AgRP), Leptin receptor (OB-R), Melanocortin 4 receptor (MC4R) and Insulin receptor (INSR) in the hypothalamic region as well (B). In contrast we were able to show a lower expression of pro-opiomelanocortin (POMC) of hypothalamic neurons (B), which are important for the central regulation of satiety.
Data are expressed as mean ± SEM, n ≥ 7 animals per group;
*p < 0.05 and t-test.

Summary

- Exposure of the dams to BuP during pregnancy and breastfeeding increases body weight, fat mass and adipocyte area in female offspring. These effects are only detectable in the female but not in the male offspring.
- Perinatal exposure leads to an increased food intake and blood glucose level. We assumed that food intake is increased due perturbation of hypothalamic regulation of satiety.
- Our results from murine model correlates with the results of the LINA mother-child cohort of the UFZ Leipzig. They found that maternal paraben exposure due cosmetic product consumption containing BuP was linked to a higher BMI in children. They conclude that cosmetic product consumption during pregnancy is linked to prenatal paraben exposure of children and increases obesity risk in the offspring.

Conclusion

Our data demonstrate that perinatal exposure to n-Butyl paraben leads to an increased body weight only in female offspring probably mediated by a paraben-induced higher body weight which is coupled with higher fat mass and glucose levels. Furthermore maternal exposure increases food intake in female offspring that may be explained with a disturbed neural regulation of satiety in the hypothalamus. These data implicate that parabens may cause the development of obesity in female offspring by perturbation of regulation of satiety and hunger.

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