

Sexually dimorphic effect of gestational exposure to BPA on DNA methylation pattern in the rat placenta.

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Changes in placental physiology following exposure to environmental factors such as endocrine disruptors, trigger an adaptive response. This supports the involvement of placenta in programming, and as such, its possible significance for subsequent adult health, otherwise termed developmental origin of health and disease (DOHaD). It has been reported that the sex of embryos may have an impact on how the placenta will respond to environmental “stressors”.

Epigenetic mechanisms can affect gene expression and thereby predispose to some diseases even after cessation of exposure to an environmental factor. We hypothesized that alteration of DNA methylation in the placenta could provide early markers of exposure to endocrine disruptors. We aimed at studying the effect of a gestational exposure to Bisphenol A, a largely widespread endocrine disruptor, on DNA methylation pattern in female and male rat placenta.

Pregnant rats were exposed orally to BPA (10mg/kg/d) from gestational day 6 (GD 6) to 18. Placentas obtained by cesarean section were harvested at GD 19. Male and female placentas were identified using classical PCR for SRY expression. Genome-wide DNA Microarray analysis was performed to identify genes with aberrant methylation following gestational exposure. Additionally, possible changes in expression of DNA methyltransferases (DNMT1 and DNMT3a), enzymes that catalyze DNA methylation, were examined by RT-PCR in male and female placenta.

In female placenta, we identified a small number of genes that exhibited hypermethylation after BPA exposure with statistical significance (adjusted p-value < 0.05): SF-1 (log Fold Change : 1,21) ; Hmx2 (log FC : 1,36) ; Tctn2 (log FC : 1,45) and Mamdc4 (log FC : 1,14). In male placenta, one gene was significantly hypermethylated: Tnks2 (log FC : 1,92).

For DNMT3a expression, BPA exposure led to a sex-specific response since DNMT3a mRNA levels were significantly increased in male but not in female placenta. There was no effect of BPA on DNMT1 mRNA levels neither in male and female placenta.

In conclusion, prenatal exposure to a high dose of BPA lead to changes in DNA methylation pattern of various CpG islands in a sexually dimorphic manner, highlighting sex specific effects of early endocrine disruptor exposure on placental function that could be consistent with increased risk of disease later in life.

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