Sexually dimorphic methylation of SF-1 gene in rat placenta after gestational exposure to BPA

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Introduction

The long latency between exposure to endocrine disruptor chemicals (EDCs) and effects later in life leads to a need for early biomarkers of exposure that could justify the protection of pregnant women and fetuses against EDCs adverse effects. At the interface between the mother and the foetus, the placenta plays a key role in fetal programming and responds to environmental stressors in a sex specific manner. Epigenetics has appeared to be a key mechanism for regulation of gene expression in response to early life environment.

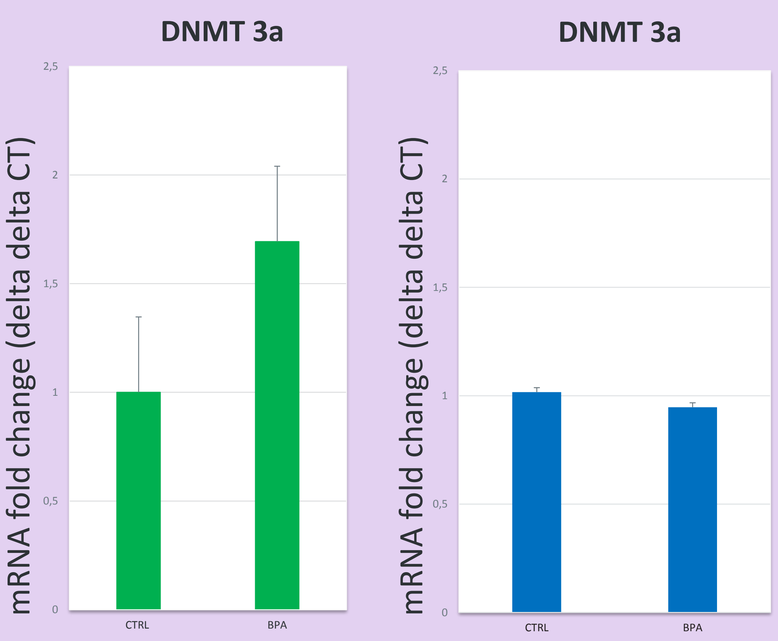
We hypothesized that changes in placental DNA methylation could provide early markers of exposure to EDCs.

Materials and Methods

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

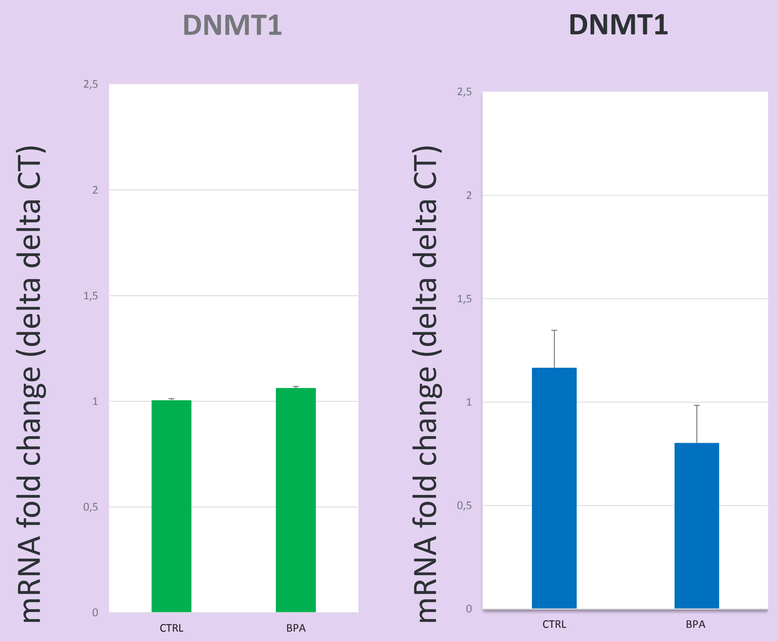
Results

Sexually dimorphic effect of exposure to BPA on mRNA expression of DNMT 3a



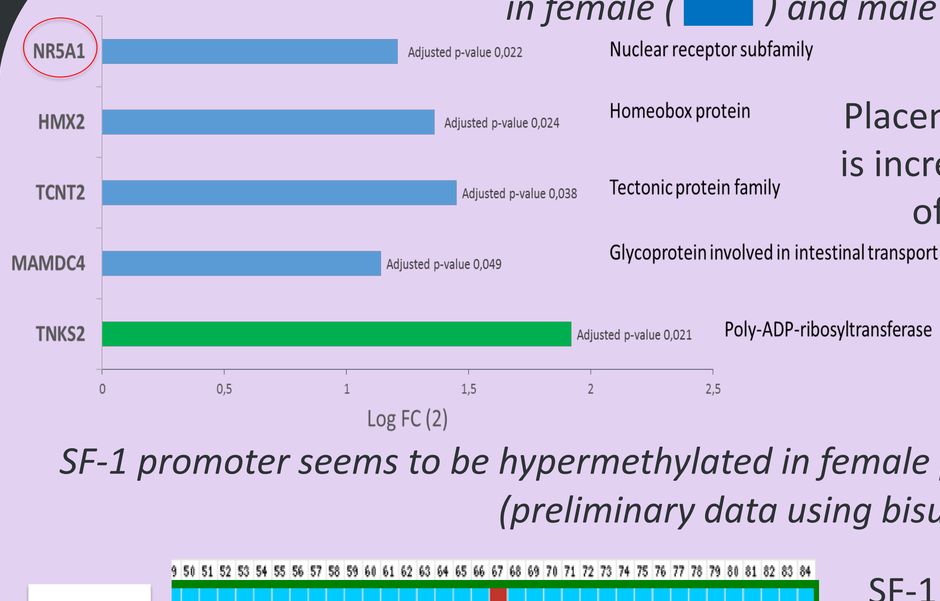
Male placenta (n6) Female placenta (n5)

No effect of exposure to BPA on mRNA expression of DNMT 1



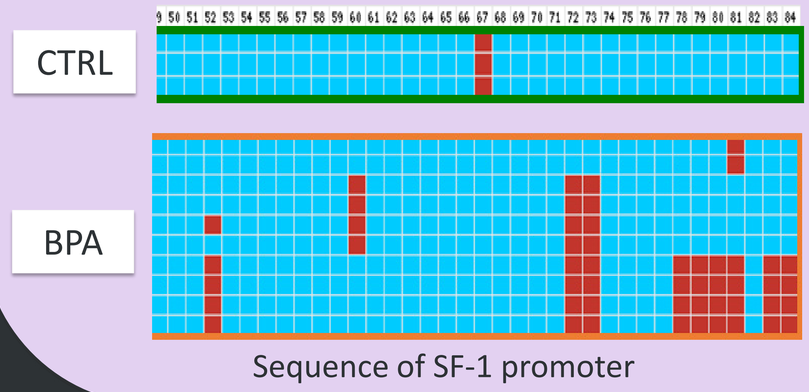
Male placenta (n6) Female placenta (n5)

Genes hypermethylated after gestational exposure to BPA in female (■) and male (■) placenta



Placental DNA methylation of various CpG islands is increased after prenatal exposure to a high dose of BPA with a sexually dimorphic manner

SF-1 promoter seems to be hypermethylated in female placenta after gestational exposure to BPA (preliminary data using bisulfite sequencing)



SF-1 gene, a key factor in the development and the function of the ovaries appears to be a placental epigenetic target of prenatal exposure to a high dose of BPA in female placenta

Conclusion

SF-1, a key regulator of sexual development appears to be a good placental epigenetic biomarker of gestational exposure to BPA and could mediate the adverse effects of BPA on the reproductive system

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