An animal model for prenatal stress and offspring impairment: Prenatally traumatized mice reveal hippocampal methylation and expression changes of the stress-related genes Crhr1 and Fkbp5.

Anne-Christine Plank1, Stefan Frey2, Lukas Basedow2, Jalal Solati1, Fabio Canneva1, Stephan von Hörsten3, Oliver Kratz2, Gunther H. Moll1, Yulia Golub2

1. Department of Child and Adolescent Mental Health, University Hospital Erlangen, 91054 Erlangen, Germany
2. Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, 01307 Dresden, Germany
3. Department Experimental Therapy, University Hospital Erlangen, 91054 Erlangen, Germany

Background

Recently, we showed that prenatal trauma (PT) exposure in mice leads to an anxiety phenotype associated with a smaller body size, increased corticosterone (CORT) and anxiety-like behavior in pups. The present study was conducted to understand the mechanisms by which aversive in utero experience leads to these long-lasting behavioral and neuroendocrine changes, investigating whether (1) prenatally traumatized mice (PT mice) display increased basal and stress-induced CORT levels; (2) changes in CORT levels are accompanied by changes in the expression and methylation levels of key HPA axis regulatory genes and (3) PT-induced changes in the expression levels of HPA axis regulatory genes can already be detected in fetuses following PT.

Methods

Maternal trauma (MT) was induced by an electric foot shock at gestational day (GD) 12. Basal and stress-induced (stressor: elevated plus maze (EPM) testing) serum CORT levels were assessed in PT/no PT mice at postnatal day (PND) 150 and in MT/no MT mothers one week after weaning. The dorsal hippocampus (dHPC) of PT/no PT mice was isolated for methylation and gene expression analyses of Crhr1, Fkbp5, Nr3c1 and Nr3c2 (A). The latter were additionally performed on dHPC samples isolated from PT/no PT fetuses on GD 18 (B).

Results

Both basal and stress-induced serum CORT levels were higher in MT/PT than in no MT/no PT mice, respectively (A).

We also found increased corticotropin-releasing hormone receptor 1 (Crhr1) and decreased FK506 binding protein 5 (Fkbp5) mRNA levels in the left dHPC of adult PT mice. These alterations were accompanied by a decreased methylation status of the Crhr1 promoter and an increased methylation status of the Fkbp5 promoter, respectively (B).

Interestingly, the changes in Fkbp5 and Crhr1 mRNA levels were not detected in the embryonic dHPC of PT mice (C).

Discussion & Conclusion

We show that maternal traumatic experience causes HPA axis dysregulation, manifesting in increased basal and stress-induced CORT levels both in traumatized mothers and their offspring. Since it has been suggested that higher levels of CRHR1 induce an anxiety-like phenotype in rodents, our finding of increased Crhr1 expression corroborates a potential role of Crhr1 in the higher risk of developing psychopathologies after prenatal trauma. However, the finding that hippocampal expression levels of Fkbp5 were decreased in PT mice was unexpected and needs further investigation.

Together, our findings provide evidence that prenatal trauma has a long-term impact on stress axis function and anxiety phenotype associated with altered Crhr1 and Fkbp5 transcripts and promoter-methylation.

References


Contact: Dr. Anne-Christine Plank (anne-christine.plank@uk-erlangen.de), Department of Child and Adolescent Mental Health, University Hospital Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany

Funding: “Erlanger Leistungsbezogene Anschubfinanzierung und Nachwuchsförderung” and “Nachwuchsforde”rung, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU).