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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*.

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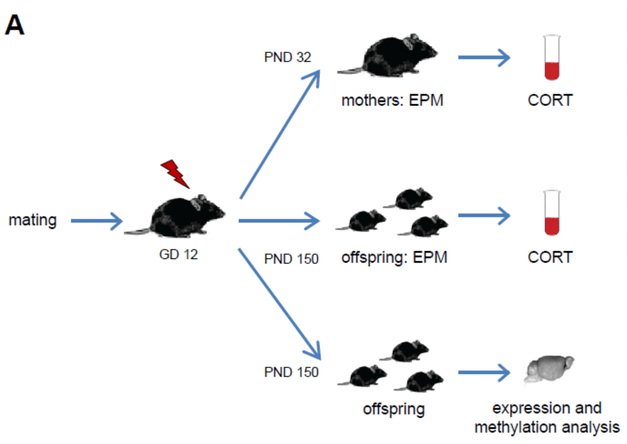
Background

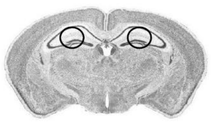
Recently, we showed that prenatal trauma (PT) exposure in mice leads to an anxiety phenotype associated with a smaller body size, increased corticosterone (CORT) and anxiety-like behavior in pups[1]. The present study was conducted to understand the mechanisms by which aversive *in utero* experience 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

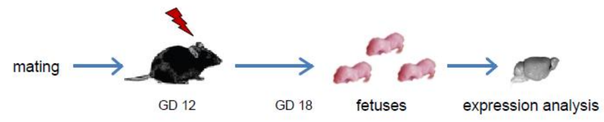
A



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**).

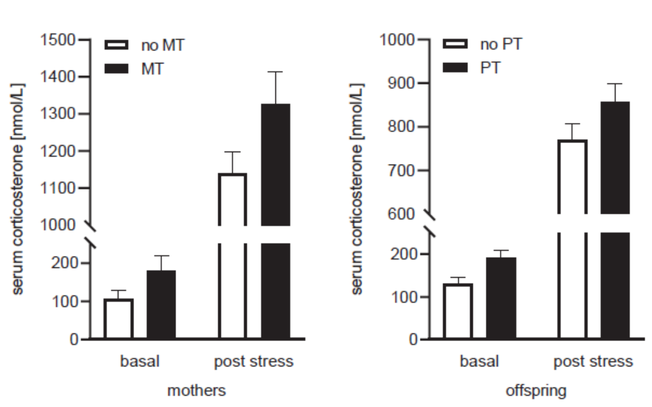


B



Results

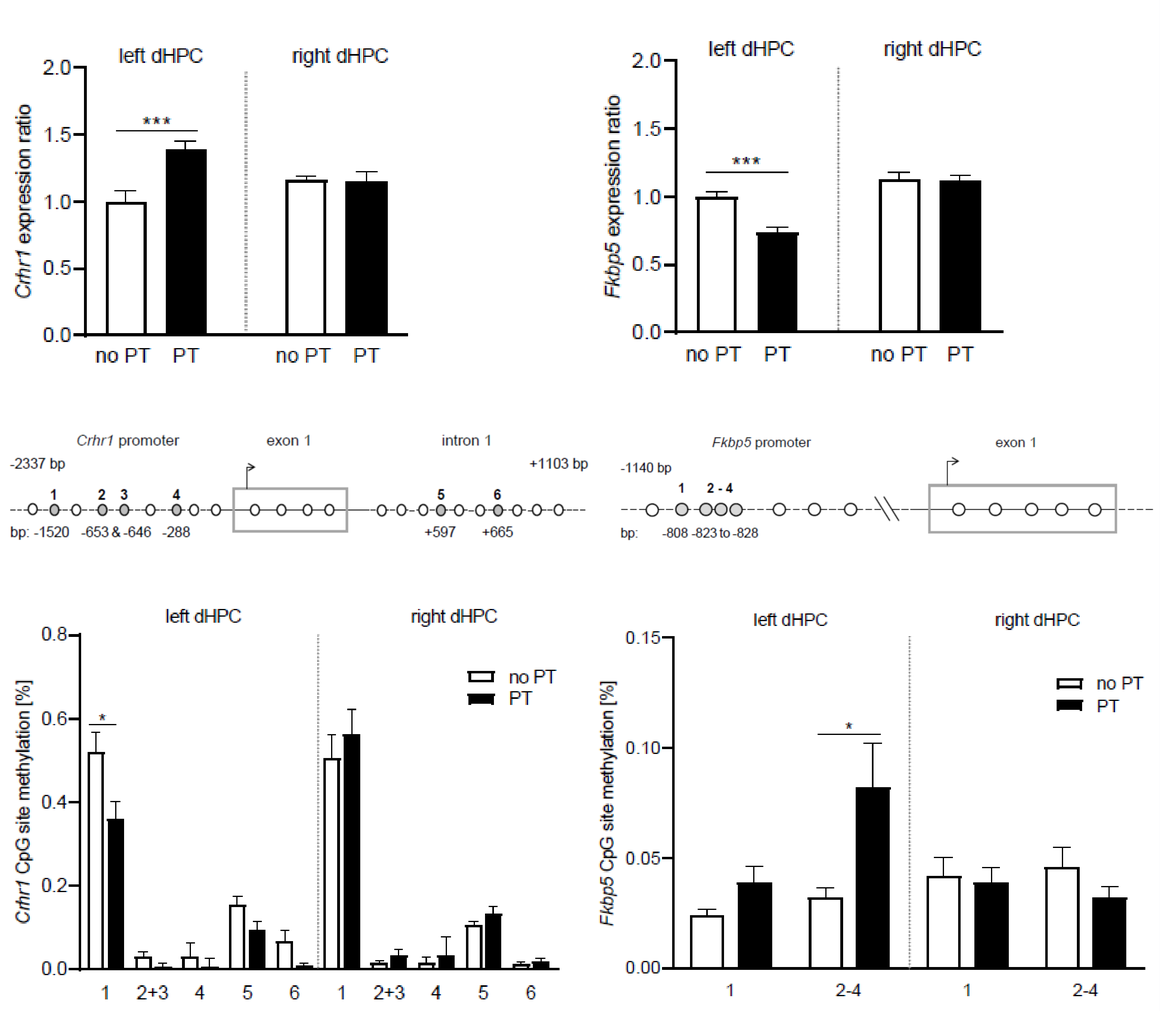
A



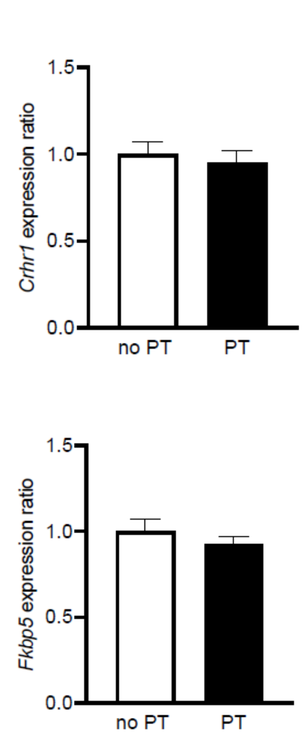
Both basal and stress-induced serum CORT levels were higher in MT/PT than in no MT/no PT mice, respectively (**A**).

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**).

B



C



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[2], 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

Study results were published in: Plank AC, Frey S, Basedow LA, Solati J, Canneva F, von Hörsten S, Kratz O, Moll GH, Golub Y. Prenatally traumatized mice reveal hippocampal methylation and expression changes of the stress-related genes Crhr1 and Fkbp5. Transl Psychiatry. 2021 Mar 23;11(1):183. doi: 10.1038/s41398-021-01293-y. PMID: 33758173; PMCID: PMC7988147.

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