Neuroinflammation and hepatic inflammatory processes heighten vulnerability to psychopathology in adolescent rats exposed to stress early in life.

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Background

It is well known that stress early in life (ELS) is one of the major risk factors for psychiatric disorders. At preclinical level, the prenatal stress (PNS) model has been widely used to mimic early adversities and has been shown to have long-term effects on brain function. Recent studies reported that ELS may also lead to metabolic conditions such as insulin resistance, often in comorbidity with mental disorders. While the precise biological pathways deregulated by ELS, which may contribute to the development of such comorbidities, remain incompletely understood, an abnormal inflammatory response is emerging as a primary mechanism. The interplay between the brain and liver, both pivotal in metabolic regulation, underscores the significance of this mechanism as several inflammatory mediators released in the liver can reach the brain and trigger a pro-inflammatory response that leads to behavioral changes.

Can a combined inflammation in liver and hippocampus represent a key element in mediating vulnerability to stress exposure during gestation?

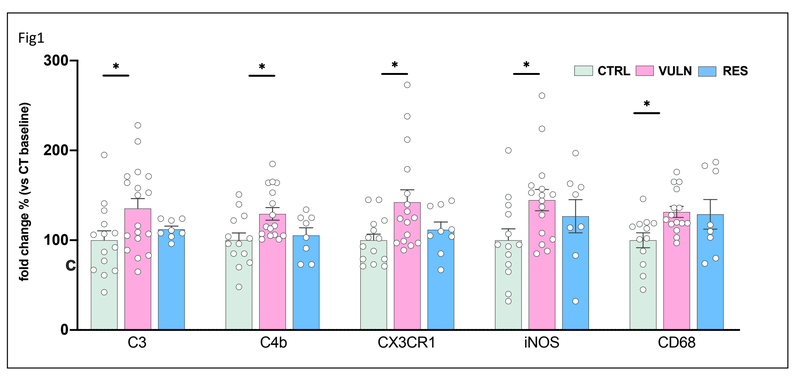
Keywords: mood disorders, neuroinflammation, ELS, liver-brain axis

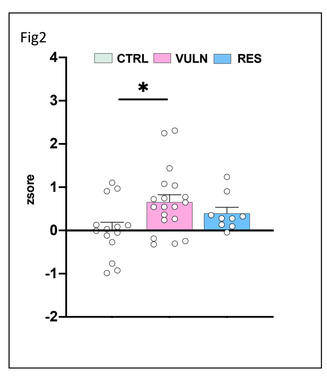
Methods

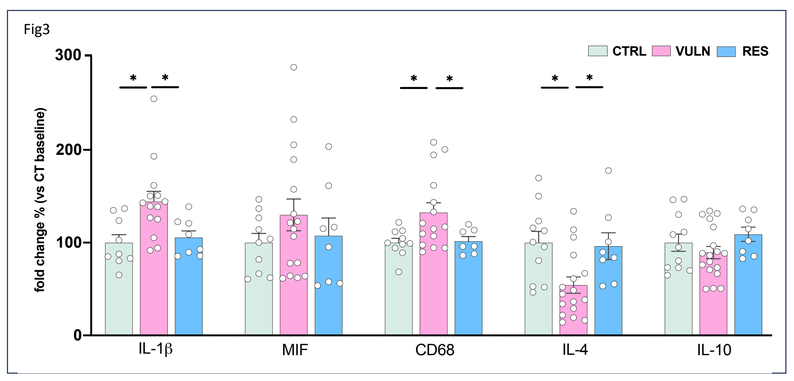
Pregnant rats were subjected to the PNS paradigm during the last week of gestation (restraint under bright light for 45 minutes, three times a day). In adolescence, male and female offspring were assessed for various psychopathological domains and then euthanized. We used a two-step cluster analysis, based on behavioral tests (social interaction, sucrose preference, and novelty suppressed feeding) to classify animals as vulnerable or resilient to PNS. Dorsal hippocampus and liver were dissected, and total RNA was isolated and used for real-time PCR analyses to assess gene expression of microglia activation markers in brain, inflammatory mediators and Leptin receptor (LepR) in liver.

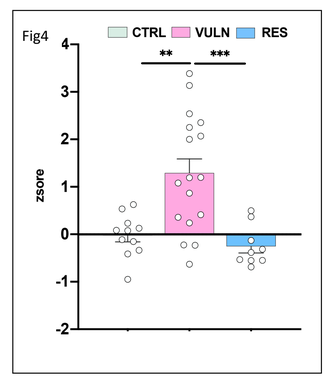
Results

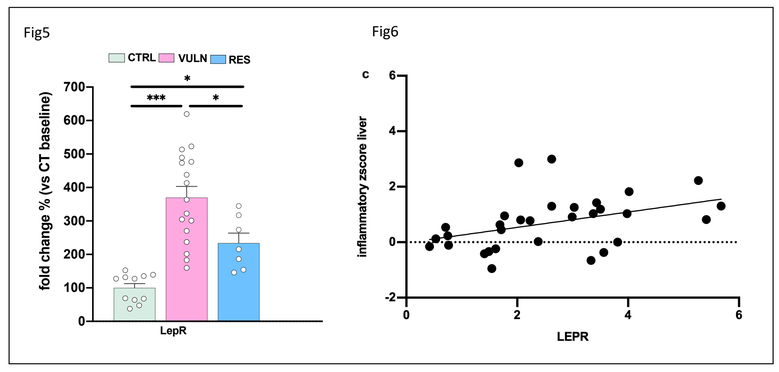
In dorsal hippocampus, microglial activation markers were differentially expressed in male adolescent rats vulnerable to prenatal stress as compared to the control group. In addition, the same vulnerable animals showed an abnormal inflammatory response in the liver, indicating the presence of a systemic inflammation. Notably, this effect correlates with an increased expression of Leptin receptor in the liver of vulnerable males as compared to controls. A correlation analyses between expression of LepR and the inflammatory mediators is shown in figure 7, considering only the vulnerable animals. No significant changes were found in female adolescent rats neither in brain nor in liver.

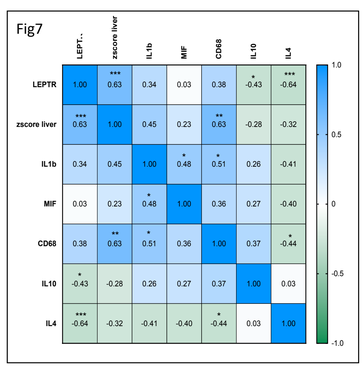












Conclusion

In this study, we demonstrated that the activation of microglia in the dorsal hippocampus, along with the dysregulation of inflammatory responses in liver and an increased expression of Leptin receptor, may constitute biological processes, within the framework of the brain-liver axis, that could lead to multimorbidity as a result of exposure to ELS, contributing to the development of a vulnerable phenotype.

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