P0029 / #2702

Topic: AS01 Nervous System Development and Related Disorders

THE EFFECT OF MATERNAL CORTISOL ON OFFSPRING'S BRAIN DEVELOPMENT

Aline Camargo Ramos [1], Pratik Kashyap [2], Ana Carolina Milani [1], Célia Araújo [1], Lucas Pinto Ribeiro [1], Ivaldo Silva [3], Cristiane Duarte [4], Jonathan Posner [2], Andrea Jackowski [1]

[1] *UNIFESP, Psychiatry, São Paulo, Brazil*
[2] *Duke University, Psychiatry And Behavioral Sciences, Durham, United States of America*
[3] *UNIFESP, Ginecology, São Paulo, Brazil*
[4] *Columbia University, Child And Adolescent Psychiatry, New York, United States of America*

Exposure to adverse childhood experiences (ACEs) can result in altered regulation of the hypothalamic-pituitary-adrenal (HPA) axis as evidenced by altered cortisol levels. Stress-induced increase in maternal glucocorticoid levels during pregnancy may lead to fetal glucocorticoid overexposure which can affect brain development, and alter HPA axis development. The present study investigated whether maternal cortisol levels impact neonate cortisol levels and brain development. Salivary cortisol was collected from mothers and their offspring on the same day that the neonates performed a brain MRI scan. Multiple linear regressions were conducted for 14 bilateral subcortical regions (hippocampus, amygdala, caudate, putamen, globus pallidus, thalamus, and accumbens) as dependent variables with maternal cortisol as the independent variable and controlled for post-menstrual age (PMA) and infant sex. The subcortical regions were segmented using a validated infant MRI platform (finneas.ai). The results were corrected for multiple comparisons using the Bonferroni correction ($p < 0.004$; 14 different models). The correlation between maternal and infant salivary cortisol levels was also explored. A total of 130 dyads (mothers and neonates) were included in the analyses. The average age for the mothers was 27.03 (±5.17) years-old and for the neonates was 43.7 (±1.64) days (postmenstrual age – PMA) at MRI. Average maternal cortisol level was 5.23 (±4.27) ng/mL and the neonate's salivary cortisol was 8.87 (±7.42) ng/mL. Maternal cortisol level was negatively correlated with the volume of the left hippocampus ($p < 0.004$). There was a strong correlation between maternal and neonate cortisol levels ($p = 0.0001$). Our results suggest synchronicity between maternal and neonatal cortisol, suggesting an influence of maternal stress in offspring HPA axis development. Moreover, our data demonstrated that increased maternal cortisol is related to offspring brain development, specifically in the left hippocampus, a brain region rich in glucocorticoid receptors.

Declaration of Interest Statement: None

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Topic: AS01 Nervous System Development and Related Disorders

HISTONE H4 ACETYLATION INVOLVEMENT IN SEXUALLY DIMORPHIC AROMATASE EXPRESSION OF DEVELOPING MOUSE BRAIN

Camila Sosa [1], Lucas Cabrera Zapata [2], Carla Daniela Cisternas [1], Maria Ángeles Arévalo [2], María Cambiasso [1]

[1] *Instituto Ferreyra, INIMEC-CONICET-Universidad Nacional de Córdoba, Neurophysiology, CORDOBA, Argentina*
[2] *Cajal Institute - CSIC, Functional And Systems Neurobiology, Madrid, Spain*

During early development, sex chromosome complement (SCC) regulates a sexually dimorphic gene expression in limbic regions of the mouse brain. Furthermore, aromatase and ERβ expression are higher in amygdala neurons of XY than XX embryos at embryonic day (E) 15, before of critical period of hormone-induced brain masculinization. Epigenetic has been proposed as mediator of hormonal and genetic sexual differentiation of the brain. We aimed to study the role of SCC on the epigenetic mechanisms involved in brain sexual differentiation. Four core genotypes mouse model (FCG) was employed to evaluate by RT- qPCR the epigenetic machinery involved in DNA methylation and histone deacetylation in amygdala at E15. Moreover, the epigenetic regulation of aromatase and ERβ expression was analyzed by Chromatin Immunoprecipitation (ChIP-qPCR) from E15 amygdala primary neuronal cultures segregated by sex using anti-Acetyl-H3 and -H4 antibodies. Independent cultures were performed to evaluate the effect of pharmacological inhibition of DNA methylation (using zebularine) on the aromatase gene expression by RT-qPCR. We found that SCC regulate the sexually dimorphic expression of *de novo* DNA methyltransferase 3a and 3b, and histone deacetylase 2 and 8 with higher expression in XX than XY embryos. Zebularine did not change aromatase expression levels neither in male nor female cultures. However, ChIP assays showed an enrichment of Acetyl-H4 in the male aromatase promoter that was not observed in female cultures. The ERβ promoter did not show a significant enrichment of the explored marks. In summary, the acetylation of H4 could be contributing to relax chromatin structure in male amygdala neurons, thereby facilitating the access of the transcriptional machinery to the aromatase gene promoter leading to the higher expression previously observed in males. These results contribute to a better understanding of the role of epigenetics in the establishment of brain sex differences independently of hormonal masculinization.

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