

PO28

Sex differences in early life programming of the hypothalamic-pituitary-adrenal axis in humans suggest increased vulnerability in females

Thomas Carpenter*, Sheila Grecian, Rebecca Reynolds

Endocrinology Unit, University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, Edinburgh, UK



Overexposure of the developing fetus to glucocorticoids is a key mechanism linking early development with later life disease. In humans low birthweight, a marker of an adverse in utero environment, associates with increased fasting cortisol, increased hypothalamic-pituitary-adrenal (HPA) axis reactivity and with cardiovascular risk factors, cardiovascular disease and poorer cognitive function. Animal models suggest the HPA axis of female offspring is more susceptible to programming insults. We hypothesised that there would be similar sex differences in humans. We carried out a systematic review, searching Embase, Medline and Web of Science up to June 2014. Two independent researchers screened articles for eligibility. The 29 included studies investigated the consequences of maternal stressors of asthma, psychosocial stress and glucocorticoid medications on HPA axis outcomes of placental glucocorticoid biology, and HPA axis function in early- and later-life. Overall, the studies reported sex differences such that female offspring were more responsive to stress both in early- and later-life: females had lower birthweight, increased therapeutic responsiveness to glucocorticoids, increased diurnal cortisol secretion and HPA axis reactivity, compared to males. Further, in comparison to males, the female placenta increased its permeability to maternal glucocorticoids following maternal stress with downregulation of the enzyme 11-beta-hydroxysteroid dehydrogenase (which converts active cortisol to inactive cortisone) in response to maternal glucocorticoid exposure or maternal asthma. The observations of increased programmed vulnerability of the HPA axis in females is consistent with data from animal models and may be a mechanism underlying sex differences in later life diseases including depression and cardiometabolic disease.

<http://dx.doi.org/10.1016/j.psyneuen.2015.07.476>

PO29

Maternal early life adversities and the offspring's epigenome: A M.A.V.A.N. project

Eva Unternaehrer^{1,2,*}, Kieran O'Donnell^{1,2}, Andrée-Anne Bouvette-Turcot^{1,2}, H       Gaudreau², Katherine Cost³, Alison Fleming³, Mair Steiner³, Julie MacIsaac⁴, Sarah Mah⁴, Lisa McEwen⁴, Michael Kobor⁴, Li Chen⁵, Hong Pan⁵, Wu Yong Hui⁵, Joanna Holbrook⁵, Michael Meaney^{2,5}, Study Team MAVAN²

¹ McGill University, Montr      , Canada

² Douglas Mental Health University Institute, Montr      , Canada

³ University of Toronto Mississauga, Toronto, Canada

⁴ Centre for Molecular Medicine and Therapeutics, Vancouver, Canada

⁵ Singapore Institute for Clinical Sciences, Singapore, Singapore



Background: Offspring of mothers exposed to early life adversities, such as childhood maltreatment or an adverse parental rearing environment, have a higher risk for physical and mental disorders later in life. Examining adaptations in the offspring's epigenome might provide insight into the underlying mechanisms.

Methods: We included 200 children, aged 8 to 10 years from two cohorts of mothers recruited in Montreal and Hamilton as part of the M.A.V.A.N. project. We assessed child DNA methylation profiles using the Illumina HumanMethylation 450K Bead Chip array. Maternal adversity scores were calculated based on maternal childhood abuse and neglect (Childhood Trauma Questionnaire) and maternal care (Parental Bonding Instrument). After preprocessing, principal components were extracted from DNA methylation values. Effects of ethnicity, gender, maternal adversity and interaction between gender and maternal adversity on DNA methylation principal components were tested using ANCOVA. CpG clusters with highly correlated DNA methylation values were extracted by applying a "Weighted Gene Co-Expression Network Analysis" approach to examine whether maternal early adversities predict DNA methylation in distinct gene networks.

Results: Preliminary analyses indicate an interaction between maternal early adversity and offspring gender predicting variation in DNA methylation ($F(1)=7.185$; $p=0.008$). Gene cluster analysis and module identification reveal underlying biological systems where epigenetic modifications might reflect maternal developmental history.

Discussion: The results suggest that maternal developmental history is reflected in the epigenome of the offspring. Gene network analysis reveals underlying functional systems that are epigenetically programmed in association with maternal early life adversity.

<http://dx.doi.org/10.1016/j.psyneuen.2015.07.477>