RESEARCH COMMENTARY

Sex-biased transgenerational effect of maternal stress on neurodevelopment and cognitive functions

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Given the gestational conditions in mammals, the physiological changes of the mother are likely to have a profound effect on the growing fetus, especially on the neurodevelopmental processes and neuronal functions. In rats, for example, prenatal overexposure to a few hormones is known to bring about drastic behavioral changes in the offspring (Berenbaum and Bleitz, 2011). Similar observations are also observed in humans. For example, mothers affected with diabetes, obesity and/or overweight during pregnancy are likely to be predisposed to have offspring with neurodevelopmental disorders, including autism, schizophrenia, and attention-deficit/hyperactivity disorders (Torres-Espinola *et al.* 2015; Ornoy *et al.*, 2001). It is intriguing however that the male children are at a higher risk of developing such neurodevelopmental disorders (Bloom *et al.*, 2011), though the molecular mechanism behind such sex-specific effect

of maternal stress has not been very well understood. A recent study using a murine model, published in the July issue of the journal *Biological Psychiatry* (Bronson *et al.*, 2017), demonstrated that the male sex-specific epigenetic alterations, impaired placental metabolic functions, and delayed cortical development could underlie the abnormal behavioral phenotype observed in the offspring born to stressed mothers. Thus, this commentary is essentially to discuss the significance of this study in terms of understanding the mechanism behind the gender-biased influence of maternal health during pregnancy that affects across generations.

Various studies have indicated that maternal prenatal physiological/psychological insults have an adverse effect on offspring and some of them seem to have a differential effect based on the sex of the offspring. For example, in a human-based study, females exposed to a higher level of prenatal cortisol exhibited significantly more negative emotionality as compared with males that had a similar exposure to prenatal cortisol (Braithwaite *et al.*, 2017). Whereas in other studies prenatal stress induces reduction in adult neurogenesis in males (Lemaire *et al.*, 2000; Mandyam *et al.*, 2008; Morley-Fletcher *et al.*, 2011; Belnoue *et al.*, 2013; Madhyastha *et al.*, 2013), but does not seem to affect the neurogenesis in females (Mandyam *et al.*, 2008; Zuena *et al.*, 2008). In mice model, the male offspring exposed to prenatal stress showed heightened hypersensitivity, anxiety and behavioral disorders (Mueller and Bale, 2008). At the molecular level, stress early in pregnancy significantly increased the expression of the genes coding for peroxisome proliferator-activated receptor alpha (PPARα), insulin-like growth factor binding protein 1 (IGFBP-1), hypoxia-inducible factor 3 α (HIF3α), and glucose transporter 4 (GLUT4) in the placenta males but not in females. One of the possible mechanisms of this differential expression is thought to be epigenetic regulation (Weaver *et al.*, 2004). For instance, prenatal stress was shown to cause a significant elevation in DNA methyltransferase 1 (DNA methylation

enzyme) expression in the placenta of females, but not in males. Prenatal stress reduced epigenetically regulated hippocampal glucocorticoid receptor and increased amygdalar corticotrophic releasing factor expression in the male brain only (Mueller and Bale, 2008). However, what are the triggers that modulate the epigenome, and how the differential epigenome might regulate the neurodevelopmental process were not unequivocally established. The recent study of Bronson *et al.* (2017) demonstrated as to how maternal metabolic disorders like obesity and diabetes could bring about sex-specific changes in the insulin signaling pathways in the placental tissue and the neurodevelopmental process of growing fetus.

Placenta plays an important role throughout pregnancy and insulin is known to dynamically regulate the placental function (Bronson and Bale 2016; Myatt, 2006). Intriguingly, the study of Bronson *et al.* (2017) showed that perturbations in insulin signaling in the placental tissue have a profound effect on the male offspring, suggesting a sex-specific change in the developmental process. To find out the mechanistic link behind such gender-biased outcome of maternal physiological stress, the authors used the Cre/loxP system to conditionally knockout the insulin receptor in the fetally-derived placental trophoblasts – the cells forming the outermost layer of a blastocyst. The authors showed that the insulin deficiency (due to the lack of receptor) in placental tissue resulted in the neuroendocrine stress (hypothalamic-pituitary-adrenal axis), leading to impaired sensorimotor gating and defective mitochondrial function in the prefrontal cortex of male mice only. Indeed, such impairments are seen in the pathogenesis of neurodevelopment disorders such as schizophrenia and autism (McKlveen *et al*. 2015; Selemon and Zecevic, 2015; Batandier *et al.* 2014). The authors predicted that the insulin deficiency in the placenta might affect the neurodevelopmental events exclusively in the male embryos through an epigenetic process. Indeed, the placental deficiency of insulin-induced changes in the

transcriptome of the developing embryo. Intriguingly, a subset of changes, whose changes were observed in the male embryos only, were known to be involved in the cytoskeleton dynamics and mobility, suggesting a sex-specific effect of the insulin deficiency in the placenta, possibly affecting the cell migration and/or proliferation in the developing male brain. Given that the newborns of diabetic mothers are known to exhibit delayed brain growth (Ornoy, 2005) and that they are at a higher risk of developing behavioral disorders (Nomura *et al.* 2012), the data presented by Bronson *et al.* (2017) are compelling enough to suggest a causal link between a sex-specific epigenetic reprogramming in the placenta and the behavioral patterns in males. Undoubtedly, further studies on this model could elucidate the precise mechanism by which insulin signaling in the placenta modulates the brain development, and might help in understanding the functional nexus between metabolic changes and neurodevelopmental processes during pregnancies.

Studies have shown that it is not just the metabolic stress, but other perturbations during the pre-, post- and/or neonatal periods can also have a sex-specific effect on the growing individual. For example, exposure to early trauma is associated with higher basal corticotrophin-releasing hormone levels in women as compared to men (DeSantis *et al.* 2011). Similarly, early life stressors are known to disrupt dopamine receptor function in the brain and may predispose women to develop psychopathologies during adolescence and/or adulthood (Derks *et al.* 2016). Thus the gender-specific influence of maternal stress is not only restricted to the neurodevelopment process. For example, high-fat maternal diet in rodent model showed increased glomerular and tubular kidney injury in male offspring only (Tain *et al.* 2017), though the underlying mechanisms behind such biases are not yet elucidated. With the rising incidence rate of lifestyle diseases, developing appropriate model systems to dissect the factors that

contribute to sex-specific epigenetic changes are the need of the hour, and such advancements can immensely contribute to unraveling pathophysiology of epigenetic disorders as well.

References

Batandier C., Poulet L., Hininger I., Couturier K., Fontaine E., Roussel A.M. *et. al.* 2014 Acute stress delays brain mitochondrial permeability transition pore opening. *J. Neurochem.* **131**, 314–322.

Belnoue L., Grosjean N., Ladevèze E., Abrous, D. N. and Koehl M. 2013 Prenatal stress inhibits hippocampal neurogenesis but spares olfactory bulb neurogenesis. *PLoS ONE* **8,** e72972.

Berenbaum S. A. and Beltz A. M. 2011 Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. *Front. Neuroendocrinol*. **32**, 183-200.

Bloom B., Cohen R. A. and Freeman G. 2011 Summary health statistics for U.S. children: National Health Interview Survey, 2010. *Vital. Health. Stat*. **10**, 1–80.

Braithwaite E. C., Pickles A., Sharp H., Glover V., O'Donnell, K. J., Tibu F. and Hill, J. 2017 Maternal prenatal cortisol predicts infant negative emotionality in a sex-dependent manner. *Physiol. & Behav*. **175**, 31–36.

Bronson S. L., Chan J.C., and Bale T.L. 2017 Sex-Specific Neurodevelopmental Programming by Placental Insulin Receptors on Stress Reactivity and Sensorimotor Gating. *Biol Psychiatry* **82**, 127-138.

Bronson S. L. and Bale T. L. 2016 The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology* **41,** 207–218.

Derks N. A. V., Krugers H. J., Hoogenraad C. C., Joëls M. and Sarabdjitsingh, R. A. 2016 Effects of Early Life Stress on Synaptic Plasticity in the Developing Hippocampus of Male and Female Rats. *PLoS ONE* **11**, e0164551.

DeSantis S. M., Baker N. L., Back S. E., Spratt E., Ciolino J. D., Moran-Santa Maria, M. *et al*. 2011 Gender differences in the effect of early life trauma on hypothalamic-pituitary-adrenal axis functioning. *Depress. Anxiety.* **28**, 383–392.

Lemaire V., Koehl M., Le Moal M. and Abrous D. N. 2000 Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc. Natl. Acad. Sci.* **97**, 11032–11037.

Madhyastha S., Sekhar S. and Rao, G. 2013 Resveratrol improves postnatal hippocampal neurogenesis and brain derived neurotrophic factor in prenatally stressed rats. *Int. J. Dev. Neurosci.* **31**, 580–585.

Mandyam C. D., Crawford E. F., Eisch A. J., Rivier C. L. and Richardson H. N. 2008 Stress experienced in utero reduces sexual dichotomies in neurogenesis, microenvironment, and cell death in the adult rat hippocampus. *Dev. Neurobiol.* **68**, 575–589.

McKlveen J. M., Myers B., Herman J. P. 2015 The medial prefrontal cortex: Coordinator of autonomic, neuroendocrine and behavioural responses to stress. *J. Neuroendocrinol.* **27**, 446–456.

Morley-Fletcher S., Mairesse J., Soumier A., Banasr M., Fagioli F., Gabriel C. *et al*. 2011 Chronic agomelatine treatment corrects behavioral, cellular, and biochemical abnormalities induced by prenatal stress in rats. *Psychopharmacology.* **217**, 301–313.

Mueller B. R. and Bale, T. L. 2008 Sex-Specific Programming of Offspring Emotionality following stress early in pregnancy. *J. Neurosci.* **28**, 9055–9065.

Myatt L. 2006 Placental adaptive responses and fetal programming. *J. Physiol.* **572**, 25–30.

Nomura Y., Marks D. J., Grossman B., Yoon M., Loudon H., Stone J. *et al*. 2012 Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive

development and risk of attention-deficit/hyperactivity disorder in offspring. *Arch. Pediatr. Adolesc. Med.* **166**, 337-343.

Ornoy A. 2005 Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr. Endocrinol. Rev.* **3**, 104-113.

Ornoy A., Ratzon N., Greenbaum C., Wolf A. and Dulitzky M. 2001 School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. *J. Pediatr. Endocrinol. Metab.* **14**, 681–689.

Selemon L. D. and Zecevic N. 2015 Schizophrenia: A tale of two critical periods for prefrontal cortical development. *Transl. Psychiatry.* **5**, e623.

Tain Y. L., Lin Y. J., Sheen J. M., Yu H. R., Tiao M. M., Chen C. C. *et al.* 2017 High fat diets sex-specifically affect the renal transcriptome and program obesity, kidney injury and hypertension in the offspring. *Nutrients* **9**, 357-376.

Torres-Espinola F. J., Berglund S. K., García-Valdés L. M., Segura M. T., Jerez A., Campos D. *et al*. 2015 Maternal obesity, overweight and gestational diabetes affect the offspring neurodevelopment at 6 and 18 months of age—A follow-up from the PREOBE cohort. *PLoS ONE* **10,** e0133010.

Zuena A. R., Mairesse J., Casolini P., Cinque C., Alema G. S., Morley-Fletcher S. *et al*. 2008 Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats. *PLoS ONE* **3,** e2170.