

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 foetus, especially on the neurodevelopmental processes and neuronal functions. In rats, for example, the prenatal overexposure to a few hormones is known to bring about drastic behavioural changes in the offspring (Berenbaum and Beltz 2011). Similar observations are also seen 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 (Ornoy *et al.* 2001; Torres-Espinola *et al.* 2015). 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 male sex-specific epigenetic alterations, impaired placental metabolic functions, and delayed cortical development could underlie the abnormal behavioural 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 it has been shown that 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 behavioural 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 (PPAR α), insulin-like growth factor binding protein 1 (IGFBP-1), hypoxia-inducible factor 3 α (HIF3 α), 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, details such as 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 how maternal metabolic disorders like obesity and diabetes could bring about sex-specific changes in insulin signalling pathways in the placental tissue and the neurodevelopmental process of growing foetus.

The placenta plays an important role throughout pregnancy and insulin is known to dynamically regulate placental function (Myatt 2006; Bronson and Bale 2016). Intriguingly, the study of Bronson *et al.* (2017) showed that perturbations in insulin signalling 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 foetally-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 (Batandier *et al.* 2014; McKlveen *et al.* 2015; Selemon and Zecevic 2015). The authors predicted that insulin deficiency in the placenta might affect the neurodevelopmental events exclusively in the male embryos through an epigenetic process. Indeed, the placental insulin deficiency did induce changes in the transcriptome of the developing embryo. Intriguingly, a subset of changes (changes 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 behavioural disorders (Nomura *et al.* 2012), the data presented by Bronson *et al.* (2017) is compelling enough to suggest a causal link between a sex-specific epigenetic reprogramming in the placenta and the behavioural patterns in males. Undoubtedly, further studies on this model could elucidate the precise mechanism by which insulin signalling in the placenta modulates the brain development and may 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 that 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 when 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 only in male offspring (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 unravelling pathophysiology of epigenetic disorders as well.

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