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Trangenerational inheritance of stress in adolescence: a rat model

Abstract:

Pre-reproductive stress (PRS) to adolescent female rats alters anxiogenic behavior in first- and second-generation offspring in a sex-dependent manner. PRS also leads to corticotropin releasing factor receptor 1 type 1 (CRF1) gene expression changes in prefrontal cortex (PFC) and oocytes of exposed females and in offspring brain at birth and in adulthood. Here, we asked whether PRS alters the expression of stress-associated microRNAs, which regulate gene expression, in PFC and oocytes of PRS-exposed females and in the PFC of their first- and second-generation neonate offspring . We further inquired whether maternal behavior is altered in PRS-exposed rats. Finally, we asked whether maternal treatment with the CRF1 antagonist NBI 27914 (NBI, 5 mg/ml; 5 days) or the antidepressant drug fluoxetine (FLX, 5mg/ml, 7 days) can reverse PRS-induced changes in offspring behavior and gene expression. Adolescent female rats (F0) were exposed to a 7-day stress procedure, and were then treated subchronically with NBI, FLX or vehicle (VEH). Our results point to PRS-induced changes in Crhr1-targeting, stress-related microRNA in oocytes, along with PRS-induced changes in maternal behavior. We further found that post-PRS FLX treatment increases pup mortality, and both FLX and NBI reverse some of the effects of PRS but also have independent effects on F1 behavior, gene expression and global methylation. PRS also alters the molecular and epigenetic signature in paternally derived F2 offspring. These findings extend current knowledge on inter- and trans-generational transfer of stress effects, point to epigenetic changes in stress-exposed oocytes as a potential mechanism, and highlight the consequences of post-stress pharmacological interventions in adolescence.