Sex-specific Effects of Unpredictable Variable Prenatal Stress: Implications for Mammalian Developmental Programming During Spaceflight.

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During initial exposure and adaptation to the microgravity environment, adult mammals exhibit elevated stress, mediated by the Hypothalamic-Pituitary-Adrenal (HPA) axis. In our previous studies of pregnant rats exposed to 2-g hypergravity via continuous centrifugation, we reported changes in neuroendocrine profiles including decreased corticosterone and a concomitant increase in body mass and leptin in adult male offspring. Prenatally stressed adult offspring have been shown to exhibit an elevated stress response in adulthood, therefore we hypothesized that these changes resulted from stress exposure during fetal development. Future studies examining reproduction, gestation, and development on-orbit need to consider the unique stressors of vehicle launch, the space environment, and landing on the development of the HPA axis in animals born and raised in microgravity. In this study, we utilize Unpredictable Variable Prenatal Stress (UVPS) to simulate the stressors of spaceflight by exposing dams to three different stressors: (1) White Noise, (2) Strobe Light, and (3) Tube Restraint. Stressors were applied from Gestational Day 0 (G0), following an unpredictable schedule (morning [0600-1200hrs]; afternoon [1200-1800hrs]; evening [1800-2400hrs] in 15, 30, or 60 minute durations alongside non-stressed (NS) control dams. Following parturition, pups were fostered to non-manipulated, newly parturient dams to control for differential maternal care. On postnatal day 90 (P90), we harvested the hypothalamus, pituitary, and adrenal glands, and analyzed mRNA expression of the following genes via RT-qPCR: 1) melanocortin-2 receptor (*MC2R*), *POMC*, corticotropin-releasing hormone (*CRH*) in the pituitary; 2) glucocorticoid receptor (*NR3C1*), pro-opiomelanocortin (*POMC*), corticotropin-releasing hormone (*CRH*), brain-derived neurotropic factor (*BDNF*), in the hypothalamus; and 3) *MC2R*, tyrosine hydroxylase (*TH*), steroidogenic acute regulatory protein (*STAR*), cytochrome P450scc enzyme (*CYP*) in the adrenal. The identification of sex-specific fetal programming effects on adult stress response is a key step in determining potential animal behavior on-orbit, and will guide future multi-generational studies in microgravity.

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