

Sex- and Dose-Dependent Effects of In Utero Endocrine Disruptor Exposure on Offspring Behavior and Brain Monoamines

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Exposure to endocrine disruptors (EDs), including the well-known plasticizers bisphenol A (BPA) and di(2-Ethylhexyl) phthalate (DEHP), during the highly sensitive gestational period, can produce long-lasting behavioral changes in offspring. In this study, we hypothesized that gestational exposure to BPA and/or DEHP at various doses would alter stress-related behaviors and monoaminergic activity in a region-specific manner in exposed offspring. To test this, female Sprague-Dawley dams were orally administered saline (control group - 10 µL/kg BW), BPA (5 µg/kg body weight (BW)), DEHP (5 µg/kg BW or 7.5 mg/kg BW), a combination of BPA and low-dose (LD) DEHP (5 µg BPA + 5 µg DEHP/kg BW), or a combination of BPA and high-dose (HD) DEHP (5 µg BPA + 7.5 mg DEHP/kg BW) during days 6 through 21 of pregnancy. The male and female offspring of these dams underwent a battery of behavioral tests in adulthood. Brains collected from the offspring were microdissected to obtain the medial prefrontal cortex (mPFC), paraventricular hypothalamic nucleus (PVN), and hippocampus (HC), which were analyzed for monoamine and metabolite levels using High-Performance Liquid Chromatography (HPLC). While BPA and B+D (LD) female offspring demonstrated anxiolytic effects in the Open Field Test, DEHP (HD) male offspring showed feminized anxiety-like behavior in the Elevated Plus Maze. The offspring also displayed impaired fear responses in the Shock Probe Defensive Burying (SPDB) test. Males in most ED groups buried less than their control counterparts. Furthermore, low-dose ED treatments led to a robust preference for passive coping strategies in both male and female offspring. Within the brain, male offspring in the BPA, LD and HD DEHP, and B+D (HD) groups had diminished dopamine (DA) levels in the PVN, which corresponded with their reduced SPDB burying levels. Moreover, DEHP (LD) male offspring had elevated DA turnover in the mPFC, whereas B+D (LD) female offspring had enhanced norepinephrine levels in the HC, which may underlie their behavioral outcomes in the SDPB. The findings of this study have implications for sex differences in mood and anxiety disorders following prenatal exposures to BPA, DEHP, and their mixtures.

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