Effect of DMBA exposure on ovarian chemical metabolism, DNA damage sensing and repair, and oxidative stress proteins in prepubertal mice

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The polycyclic aromatic hydrocarbon, 7,12-dimethylbenz[a]anthracene (DMBA), is formed due to combustion of organic material, and environmental exposure occurs through wildfires, cigarette smoke and exhaust fumes. Exposure to DMBA induces ovarian DNA damage, causes ovarian follicle loss and the DNA damage response is partially attenuated in obese relative to lean female mice. In the United States, obesity affects 14.7 million children and 20% of girls, and impairs oocyte quality and fertility, and is associated with precocious puberty in girls. In adult mice, obesity accelerates oxidative stress, alters ovarian chemical metabolism, and disrupts the phosphatidylinositol-3 kinase pathway. This study investigated the effect of DMBA exposure in lean and obese female prepubertal mice on ovarian proteins involved in DNA damage sensing and repair, chemical metabolism, and oxidative stress. C57BL/6J female pregnant mice were fed with chow diet (lean) or switched to a 60% high fat diet (obese) on gestational day 17 until post-natal day (PND) 21 when pups were weaned. Female pups remained on the same diet and on PND 35, each diet group received either corn oil (CT) or 1 mg/Kg of DMBA (D) for 7 days by intraperitoneal injection. Body weight was recorded twice weekly, and mice were euthanized at PND 42. Final body and tissue weights were recorded. The abundance of ovarian proteins was quantified via western blotting. Statistical analyses were performed using GraphPad Prism 10.1.2 software. Final body weight increased in the obese group ($P < 0.05$) regardless of treatment compared to lean mice. Obesity increased ($P < 0.05$) ovary, uterus, kidney, and spleen weight but decreased liver weight ($P < 0.05$). Obese mice exposed to DMBA had increased ($P < 0.05$) uterus, heart, kidney, and spleen weight ($P < 0.05$) compared to lean DMBA-exposed mice. Ovarian protein abundance of CYP2E1 and BRCA1 tended ($P < 0.1$) to be decreased while CAT, EPHX1 and GSTP1 were decreased ($P < 0.05$) by basal obesity and DMBA exposure in lean mice. In obese mice exposed to DMBA, ovarian protein abundance of EPHX1 was decreased ($P < 0.05$) compared to identically exposed lean mice. There was no effect of obesity or DMBA exposure on the ovarian abundance of γH2AX ($P > 0.05$), but obesity decreased ovarian SOD1 compared to basal and DMBA-induced levels in lean mice ($P < 0.05$). Taken together, these data suggest that DMBA exposure and changes in physiological status alter organ weight and the ovarian abundance of proteins involved in chemical metabolism, DNA damage sensing and repair and oxidative stress in prepubertal mice leading to negative female reproductive effects at early stages of reproductive life.