

Bisphenol A exposure disrupts egg development in the mouse

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Estrogen plays an essential role in the growth and maturation of the mammalian egg, and recent studies in our laboratory suggest that exposure to the estrogenic chemical bisphenol A (BPA) can profoundly disrupt this process. Our studies of BPA were initiated by the accidental exposure of control mice in our animal facility to this chemical as a result of inadvertent damage to caging materials (1). Subsequent follow-up investigations established that BPA was the cause of the sudden increase in chromosome abnormalities that we observed in eggs from control females. Further, we were able to demonstrate that we could recreate the effect by short-term, low-dose oral exposure of young females to BPA (2).

The development of the mammalian egg is an extremely protracted process; it is initiated during fetal development but not completed until just prior to ovulation in the adult female. Thus, we considered that exposure to BPA and other estrogenic chemicals during fetal, neonatal, and adult life had the potential to influence oocyte development. To assess the earliest stages of oocyte development in the fetal ovary, we exposed pregnant female mice to low doses of BPA. Unexpectedly, we uncovered a novel “grandmaternal” effect whereby exposure to BPA during pregnancy disturbs oocyte development in unborn female fetuses (3). Fetal oocytes from exposed females exhibited marked changes in the events of meiotic prophase that are necessary to produce exchanges between homologous chromosomes. We found these disturbances intriguing because studies of human aneuploidy have demonstrated a correlation between alterations in the placement of exchanges between homologous chromosomes and the likelihood of their missegregation during the meiotic divisions (4). Thus, we analyzed oocytes from mature females exposed to BPA in utero. We found that the perturbations induced by BPA exposure during fetal development were translated into a dramatic increase in chromosomally abnormal eggs and embryos (3). Thus, our results are clinically relevant because they reinforce the link between fetal

events and aneuploidy that has been postulated on the basis of studies of human trisomies (4).

BPA is thought to mimic the actions of estrogen; thus we wondered if BPA was exerting its effect on the fetal ovary via a classical estrogen receptor mediated mechanism. To test this, we studied mice carrying targeted disruptions of the two known estrogen receptors. These studies provided mechanistic insight but, surprisingly, suggested that BPA acts in the fetal ovary not by mimicking the actions of estrogen but by interfering with the function of one of the known estrogen receptors, ER β (3). Thus, our data provide evidence that estrogen, presumably acting through ER β , plays a far earlier role in oocyte development than previously suspected. Importantly, our results also raise the possibility that a variety of substances—both man made or naturally occurring—that mimic the actions of estrogen or act as estrogen antagonists may affect early oocyte development. Finally, the high levels of chromosome abnormalities in eggs and embryos induced by fetal BPA exposure represent a mechanism of aneuploidy induction that is *distinct* from that reported in our previous study of adult females exposed during the final stages of oocyte growth. Thus, our studies suggest that BPA acts on the mammalian oocyte as a potent aneugen, inducing errors in chromosome segregation by at least two separate mechanisms.

REFERENCES

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