New organ culture system reveals effects of BPA exposure on fetal mammary glands

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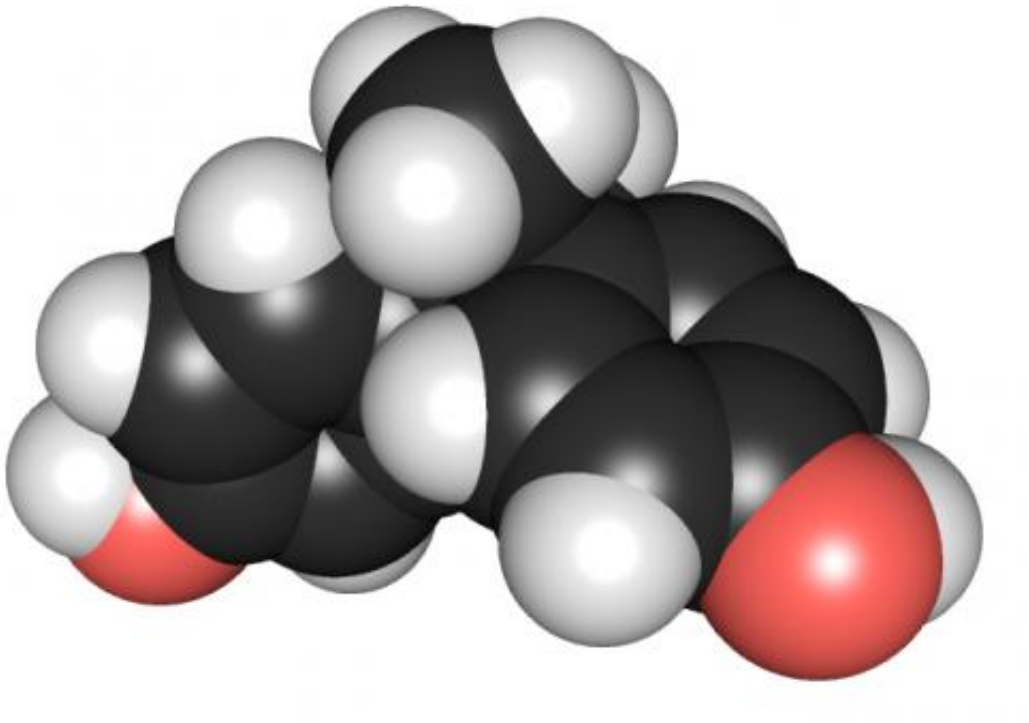

3D chemical structure of bisphenol A. Credit: Edgar181 via Wikimedia Commons

A new organ culture system developed by scientists from Tufts University School of Medicine now enables tests of the direct effects of chemical exposure, including estrogen and estrogen-like substances, on developing fetal mouse mammary tissue. Previous laboratory models

could only measure the joint effect of chemicals and maternal estrogen.

Analyses of the initial chemical investigated—bisphenol-A (BPA), an estrogen-like compound found in plastics, including food and beverage containers—revealed that BPA significantly and directly increased tissue growth in the absence of natural estrogens, when given at doses comparable to that of human exposure to BPA. Prior research in animal models has suggested that changes in fetal mammary tissue may be linked to increased risk of breast cancer in adulthood.

The study was published in *Scientific Reports* on Jan. 19.

"Our findings show that BPA, given at low doses, acts directly on the fetal mammary gland and causes similar effects observed in other animal model studies," said senior study author Ana Soto, M.D., professor in the Department of Integrative Physiology and Pathobiology at TUSM. "Because these very low, environmentally relevant levels of BPA directly affect mammary gland development, this in turn may increase the propensity to develop cancer during adult life."

"This novel bioassay enables us to answer questions that could not be addressed previously, including how these chemicals may cause abnormal organ development, a feature that is known to increase the risk of developing several diseases later in adulthood," said co-senior author Carlos Sonnenschein, M.D., a professor in the Department of Integrative Physiology and Pathobiology at TUSM.

According to a study considered representative of exposures in the U.S. conducted by the Centers for Disease Control and Prevention, BPA, which is used in the manufacture of plastics, has been found in the urine of 93 percent of Americans aged six or older. Previous research based in animal models has found that BPA, which mimics the activity of estrogen, can cause a wide range of disorders in fetuses and newborns.

Fetal exposure to BPA has been shown to alter and impair mammary gland development in mice, causing changes to lactation and increasing the risk of mammary cancer in adulthood. Until now, however, it was impossible to determine whether the observed effects of BPA were caused by its estrogen-like activity or by another mechanism, because experiments would interfere with maternal estrogens and could interrupt pregnancy.

In the current study, a team led by Soto and Sonnenschein and lead study author Lucia Speroni, PhD, research associate at TUSM, developed a novel model in which the entire mammary gland is isolated from embryonic mice and cultured in laboratory conditions similar to those in its natural environment. In the absence of maternal estrogen, this model enables investigation of estrogen and estrogen-like chemical exposure on live, developing fetal mammary tissue.

Using their new model, the team found that BPA affects fetal mammary tissue differently depending on the dose. When given at environmentally relevant levels similar to that of human exposure (1 nanomolar), BPA significantly increased the growth and branching of mammary ducts. When given at much higher levels (1 micromolar), BPA displayed the opposite activity and significantly inhibited growth.

The effect of BPA exposure was not seen when the tissue was treated with fulvestrant, an anti-estrogen compound that blocks nuclear estrogen receptors. This class of estrogen receptors has the ability to control the expression of genomic DNA. According to the authors, this finding suggests that BPA works through these receptors, but additional research is needed to reveal the precise mechanisms.

The team also tested the effect of estradiol, the natural estrogen produced by the ovaries, and found that it inhibited mammary tissue growth in a dose-dependent manner. Treatment of tissue with fulvestrant

had no effect on preventing changes caused by estradiol, suggesting that it works through a separate mechanism than BPA. By revealing functional differences between the effect of estradiol and BPA, the findings illustrate the complexity of hormone regulation in organs, write the authors.

The development of this new ex-vivo model now enables further exploration of the mechanisms by which BPA and estrogen affect developing fetal mammary tissue, as well as many other chemicals that could not be investigated before. By isolating the tissue and removing many confounding factors that are present in other models, the team hopes to gain a clearer understanding of how exposure to common hormone-modulating chemicals affects fetal development and disease in adulthood.

"We have developed an ex-vivo culture method of the fetal mammary gland, where the action of hormone disruptors such as BPA can be tested at a critical window of exposure," Speroni said. "This represents a novel approach to study the effects of hormones and hormonally-active chemicals on the developing fetal mammary tissue outside the organism."

More information: Lucia Speroni et al, New insights into fetal mammary gland morphogenesis: differential effects of natural and environmental estrogens, *Scientific Reports* (2017). DOI: 10.1038/srep40806

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