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Novel Method Identifies Potential Key Pathway in Arsenic-Induced Birth Defects

Blocking the glucocorticoid receptor (GR) pathway in a chick embryo model prevents structural birth defects induced by arsenic, according to a 2013 NIEHS-funded study at the University of North Carolina at Chapel Hill Superfund Research Program (UNC SRP). The laboratory study was performed after computationally predicting the association between the GR pathway and metal-induced birth defects with a novel approach to identify targeted biological pathways.

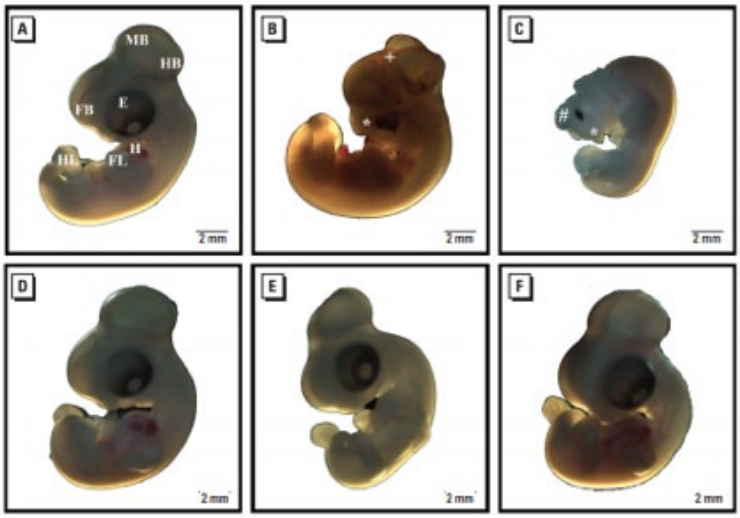
An estimated 120,000 infants are born with congenital malformations each year in the United States.[1] Of these, 60-70% are caused by unknown environmental and/or genetic causes.[2] This study focused on ways to identify biological pathways relevant to birth defects to associate environmental contaminants with human development and disease.

Researchers led by Rebecca Fry, Ph.D., selected seven metals that are known or suspected developmental toxicants and commonly found in food, drinking water, air, and/or consumer products. The scientists identified genes associated with the metals and with developmental defects using a toxicogenomics database. They then used systems level analyses to overlay the genes onto known molecular networks to represent potential metal-mediated biological pathways.

The scientists pinpointed the GR pathway as being significantly associated with development and with exposure to arsenic, cadmium, mercury, and selenium. The GR regulates genes controlling development, metabolism, and immune response. Because the pathway was altered by toxic metals and is associated with development, the researchers hypothesized that this pathway mediated metal-induced birth defects.

The research team tested these predictions in the laboratory. They used chick embryos, a model to assess developmental toxicity, to evaluate the effects of developmental exposure to arsenic.

They observed structural defects in embryos treated with levels as low as 7.5 parts per billion (ppb), which is within the 10 ppb U.S. Environmental Protection Agency maximum allowable level of arsenic in U.S. public drinking water.



Photographs of chick embryos from each treatment group showing morphological features assessed between treatment and control groups on day 6. (A) Control. (B) Embryo treated with phenytoin (PHT), a positive control for neural tube defects, exhibiting an abnormal head shape, failure of closure of the anterior part of the neural tube, and craniofacial defects. (C) Arsenic-treated embryo exhibiting craniofacial and anterior neural tube defects (anencephaly). Embryos treated with (D) cortexolone (CX), a GR inhibitor, (E) PHT plus CX, and (F) Arsenic plus CX. (Reproduced with permission from Environmental Health Perspectives)

When the team chemically blocked the GR, chick embryos did not develop structural defects when exposed to arsenic. Although the GR has been studied in relationship to metal exposures, there has been little attention to its role in birth defects. To the author's knowledge, this is the first study to examine the blocking of the GR as a means for prevention of metal-induced birth defects.

The researchers anticipate that the novel systems-biology based computational strategy can be employed to predict other biological pathways that mediate environmentally-induced birth defects. The method is cost-effective and can be used on a wide range of contaminants, generating information that may be useful in the prevention and treatment of metal-induced birth defects.

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[1] Brent RL. 2004. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by the multiplicity of environmental and genetic factors. Pediatrics 11:3957-3968.

[2] Moore KL, Persaud TVN. 1998. Human birth defects. In: Before We Are Born: Essentials of Embryology and Birth Defects. 5th ed. Philadelphia: WB Saunders Company.

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To learn more about this research, please refer to the following source:

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