TOXICOLOGICAL SCIENCES **137(2)**, 436–446 2014
doi:10.1093/toxsci/kft248
Advance Access publication November 11, 2013

Elevated Blood Pressure in Offspring of Rats Exposed to Diverse Chemicals During Pregnancy

John M. Rogers,[1] Robert G. Ellis-Hutchings,[2] Brian E. Grey, Robert M. Zucker, Joel Norwood Jr, Curtis E. Grace,[3] Christopher J. Gordon, and Christopher Lau

Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, North Carolina 27711

[1]To whom correspondence should be addressed at Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, Mail Drop B105-04, Research Triangle Park, NC 27711. Fax: (919) 541-4849. E-mail: rogers.john@epa.gov.

[2]Present Address: Toxicology and Environmental Research and Consulting, The Dow Chemical Company, 1803 Building, Midland, MI 48674.

[3]Present Address: Covance Laboratories, Greenfield, IN 46140.

Received August 1, 2013; accepted October 18, 2013

Adverse intrauterine environments have been associated with increased risk of later cardiovascular disease and hypertension. In an animal model using diverse developmental toxicants, we measured blood pressure (BP), renal nephron endowment, renal glucocorticoid receptor (GR) gene expression, and serum aldosterone in offspring of pregnant Sprague Dawley rats exposed to dexamethasone (Dex), perfluorooctane sulfonate (PFOS), atrazine, perfluorononanoic acid (PFNA), arsenic, or nicotine. BP was assessed by tail cuff photoplethysmography, nephron endowment by confocal microscopy, and renal GR mRNA by qPCR. BP was also measured by telemetry, and corticosterone (CORT) was measured in resting or restrained Dex and atrazine offspring. Treated dams gained less weight during treatment in all groups except arsenic. There were chemical- and sex-specific effects on birth weight, but offspring body weights were similar by weaning. BP was higher in Dex, PFOS, atrazine, and PFNA male offspring by 7–10 weeks. Female offspring exhibited elevated BP at 10 weeks for PFNA and arsenic, and at 37 weeks for Dex, PFOS, and atrazine. Dex, PFOS, and atrazine offspring still exhibited elevated BP at 52–65 weeks of age; others did not. Elevated BP was associated with lower nephron counts. Dex, PFOS, and atrazine offspring had elevated renal GR gene expression. Elevations in BP were also observed in Dex and atrazine offspring by radiotelemetry. Atrazine offspring exhibited enhanced CORT response to restraint. Elevated offspring BP was induced by maternal exposure to toxicants. Because all treatments affected maternal gestational weight gain, maternal stress may be a common underlying factor in these observations.

Key Words: **DOHaD; fetal programming; fetal physiology; maternal toxicity; maternal stress.**

The Developmental Origins of Health and Disease (DOHaD) hypothesis states that environmental factors in early life, including *in utero*, can alter disease susceptibility and affect physiology later in life (McMillen and Robinson, 2005). Numerous epidemiological studies have demonstrated an inverse relationship between birth weight and risk of developing cardiovascular disease and components of the metabolic syndrome in adult life, including glucose intolerance, insulin resistance, hypertension, and obesity (Lau *et al.*, 2011). Birth weight, rather than being causal, has been viewed as a surrogate for a suboptimal intrauterine environment. Maternal nutrition during pregnancy has been the environmental factor of interest in most studies of the DOHaD hypothesis, including numerous studies on offspring of women pregnant during the "Dutch Famine" of World War II (Roseboom *et al.*, 2011).

Animal models have confirmed and extended the majority of the DOHaD epidemiological findings. Although research in the sheep, guinea pig, monkey, and mouse has recapitulated aspects of the epidemiological findings (Armitage *et al.*, 2004), the rat has been used most extensively. Several rat models have been used to investigate prenatal programming of adult health parameters; these models induce intrauterine growth retardation (IUGR) through the restriction of maternal dietary intake of food (Ellis-Hutchings *et al.*, 2010), protein (Langley-Evans and Nwagwu, 1998), or specific micronutrients (Lewis *et al.*, 2001), altered uteroplacental blood flow by vascular clamping (Simmons *et al.*, 2001), or administration of the synthetic glucocorticoid, dexamethasone (Dex) (Ain *et al.*, 2005). Higher offspring systolic blood pressure (BP) has been observed following maternal under nutrition during pregnancy (Ellis-Hutchings *et al.*, 2010), and glucose intolerance and insulin resistance have been reported in adult offspring of Sprague Dawley dams treated with Dex (Buhl

Disclaimer: The research described in this article has been reviewed and approved for publication as an EPA document. Approval does not necessarily signify that the contents reflect the views and policies of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use. All funding for this research came from the Environmental Protection Agency.