Developmental Origins of Health and Disease

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Contributing Organizations: ORD: NHEERL

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LTG 3 Poster 06

Science Questions

Hypertension, Type II diabetes, and obesity are prevalent human diseases that may have a developmental origin. This concept has been termed the "Developmental Origins of Health and Disease" (DOHaD) hypothesis. Current animal tests are unlikely to detect these effects. Demonstration of latent morbidity associated with developmental exposures may necessitate new study designs to detect such effects. Our studies will characterize subsequent physiological effects of developmental exposures and have the potential to significantly improve our ability to assess developmental hazard.

This project is new since the last HHRP BOSC review. Our goal is to explore in animal models the implications of the DOHaD hypothesis for toxicity testing and risk assessment:

- Can chemical exposure during development increase risk of adult disease?
- What are the sensitive developmental periods and health endpoints?
- Are maternal undernutrition, stress and resultant fetal growth decrements common factors in adverse adult health effects?
- What are the best animal models to address these questions?

Research Goals

The goal of this project is to provide information that will ultimately lead to improvement in our ability to protect humans from potential reproductive and developmental toxicity due to adverse environmental exposures. Diabetes, obesity, hypertension, and other components of the metabolic syndrome, as well as asthma, have increased dramatically in the U.S., including in children. Our goal is to provide animal models to test the role of environmental exposures in these important human diseases. These models should be helpful in constructing hypotheses for the National Children's Study.

Conclusions

In rats, diverse agents produce lasting effects on the health of offspring at maternal dosages that affect birth weight. A consistent effect was elevated blood pressure, evident as early as seven weeks of age and persisting through at least one year of age. Effects on insulin response to glucose challenge were suggestive but inconsistent.

A key mechanism of induction of elevated blood pressure may be a lower endowment of nephrons in the kidney due to prenatal exposures or undernutrition. Renal function May also be affected by developmental Upregulation of the glucocorticoid receptor.

Birth weight deficits tended to persist postnatally, at least through weaning, and longer for some compounds."Catch-up growth" was not generally observed in offspring, nor was obesity, in rats. A transitory increase in weight was observed in offspring of pregnant mice exposed to perfluorooctanoic acid (PFOA).

Sprague-Dawley rats were more sensitive than Wistar rats to the induction of elevated blood pressure by maternal chemical treatment or undernutrition. Effects appeared earlier and more consistently in the Sprague-Dawley strain (data not shown).

The National Children's Study (See poster #08) will provide a unique opportunity to test the DOHaD hypothesis by relating developmental exposures to children's health parameters as they grow.

Brief Study Design

Pregnant animals are dosed with test chemical at the dosages and gestational periods, and by the routes, indicated in the table below. Offspring are repeatedly assessed for up to a year for noninvasive endpoints including survival, growth, blood pressure, oral glucose tolerance, female cyclicity, and hormone measures. Some animals are killed to collect tissues and organs for analysis of, e.g., kidney nephron counts and glucocorticoid receptor mRNA.

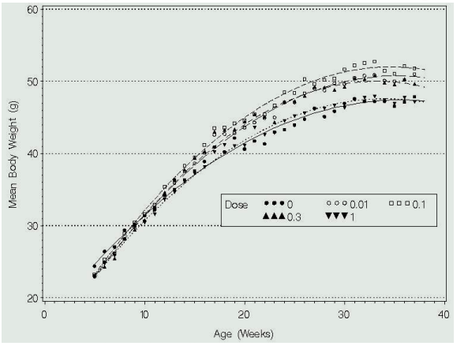
Chemicals Tested to Date

(Selected for diversity and at dosages expected to reduce birth weight)

Chemical	Use	Dose	Route	Duration
Dexamethasone	Synthetic glucocorticoid	0.6 mg/kg	Subcut. Inj.	GD 16-20
Atrazine	Herbicide	125 mg/kg	Oral	GD 16-20
PFOS	Surfactant	18.75 mg/kg	Oral	GD 2-6
PFOA (mouse)	Surfactant	0-1 mg/kg	Oral	GD 2-17
PFNA	Flame Retardant	5 mg/kg	Oral	GD 1-20
Arsenic	Water contam.	3 mg/kg	Oral	GD 1-20
Nicotine	Smoking	5 mg/kg	minipump	GD 2-20
Toluene	Solvent	1000 ppm	Inhalation	GD 9-20

completed ongoing GD= Gestation Day

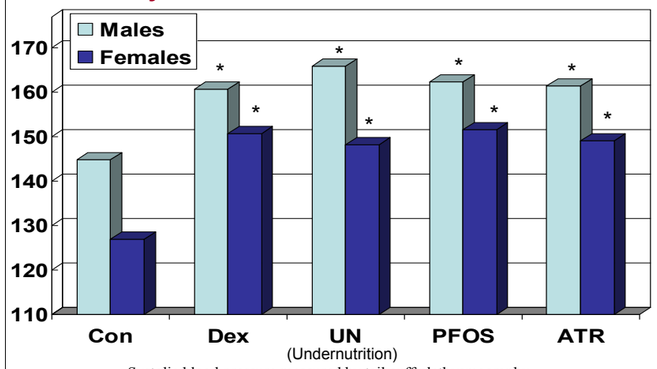
PFOA in the Mouse: Increased Body Weight in Female Offspring



Postnatal growth in offspring of pregnant mice exposed to PFOA by oral gavage on GD 2-17

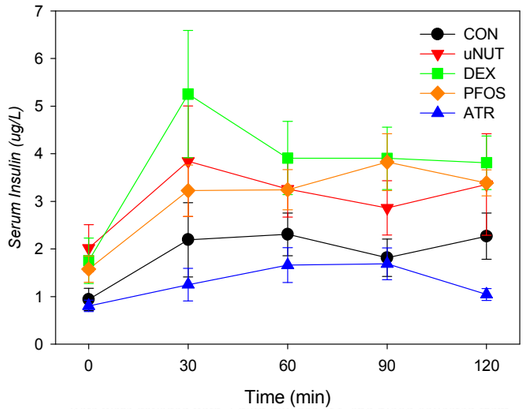
Approach/Representative Data

Systolic Blood Pressure - One Year



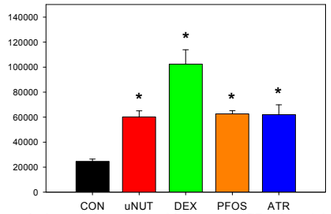
Systolic blood pressure measured by tail cuff plethysmography

Insulin Response to Glucose –One Year



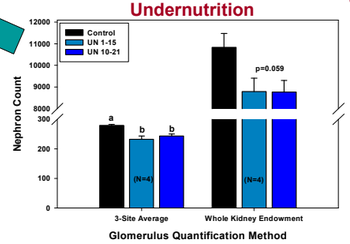
Rats were gavaged with 2 g/kg glucose at t_0 and blood collected from the tail vein at the indicated time points. Insulin measured by ELISA

Kidney GR mRNA- 17 Weeks

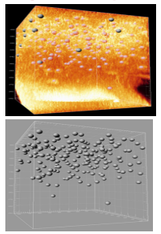


Upregulation of glucocorticoid receptor (GR, above) implicates an exaggerated hormone response which may contribute to elevated blood pressure. A reduced nephron endowment (below) may also contribute to elevated blood pressure.

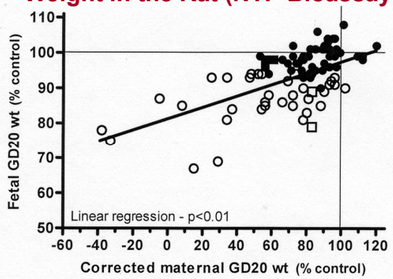
Kidney Nephron Endowment: Undernutrition



Confocal image analysis of nephrons



Relationship of Maternal and Fetal Weight in the Rat (NTP Bioassays)



In a separate study, we examined the relationship between maternal and fetal weight in 56 developmental toxicity studies done in the rat by the National Toxicology Program. Maternal weight gain was highly correlated with food intake and fetal weight, demonstrating the important role of maternal nutrition in developmental toxicity studies.

Susceptible Populations

Impact and Outcomes

- This project has the potential to change the basic study designs for assessing developmental toxicity, and to reveal latent toxic effects that current study designs will not detect.
- A small reduction in birth weight followed by postnatal "catch-up" growth has been viewed by some as a transient effect. Our data suggest that even mild effects on growth may be associated with long-term adverse health effects, regardless of catch-up growth.
- Maternal undernutrition and/or stress during gestation may be key components of fetal programming. If our data support this concept it will highlight the importance of maternal health from conception through weaning and may result in protocol changes in developmental toxicity studies that reflect these findings.

Future Directions

- Complete renal nephron counts to assess reduced nephron endowment as a possible cause of elevated blood pressure
- Assess the role of stress in the consistent effects on blood pressure using telemetry and implanted probes to measure true resting blood pressure
- Examine effects of these exposures on the epigenome of offspring, particularly promotor methylation, and associated effects on gene expression. This may represent a key mechanism for these effects.
- Explore maternal undernutrition as a common mode of action for the effects of diverse developmental toxicants on health and disease of their offspring later in life.
- Our preliminary results suggest that maternal undernutrition can lead to premature reproductive senescence in female offspring. We will follow up on this finding and expand our examination of the reproductive capacity of offspring of undernourished or chemical-exposed dams.

Researchers Involved

John Rogers, Robert Ellis-Hutchings, Neil Chernoff, Christopher Lau, Suzanne Fenton, Ralph Cooper, Tammy Stoker, Mary Gilbert, Michael Gage, Robert Zucker

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