DEER

AT A GLANCE

Title: Developmental effects of environment on reproductive health

Instrument: FP7, Environment

Total Cost: 4.615.781 €

EC Contribution: 3.499.028 €

Duration: 48 months

Start Date: 01/05/2008

Consortium: 9 partners from 7 countries

Project Coordinator: Depts. of Physiology and Pediatrics, University of Turku

Project Web Site: http://www.eu-deer.net/

Key Words: reproductive health, environment, endocrine disruption, development, gene-environment interaction, toxicogenomics, proteomics, metabolomics

THE CHALLENGE

Many of the male reproductive health issues (low sperm count, testicular cancer, low production of male hormone) are thought to arise because of maldevelopment and malfunction of the fetal testis. These reproductive disorders are thus thought to comprise a testicular dysgenesis syndrome (TDS). Several pieces of evidence suggest that common environmental chemicals, probably acting together in mixtures or in combination with other factors (genetic, lifestyle) could contribute causally to TDS. However, it is challenging to prove this rigorously.

PROJECT OBJECTIVES

The specific objectives of DEER are to approach the TDS problem by investigating:

1. connections between normal and abnormal fetal and perinatal reproductive development and subsequent maturation of reproductive function at puberty and in adulthood.

2. systemic gene-environment interactions underlying reproductive disorders taking into account genetic susceptibility, multiple exposures (mixtures of environmental chemicals and natural products) and their timing (perinatal, peripubertal, adult)

3. connections between perinatal reproductive development and metabolic disorders in later life (obesity)

Methodology

DEER takes advantage of existing human birth cohorts/samples with their associated chemical exposure analyses. Established animal and *in vitro* models are used to improve our understanding of fetal testis development and function and its relationship to male reproductive health. The complexity of real-life chemical exposures will be tackled by new bioinformatics approaches for assessing associations between exposures and reproductive disorders in humans:

Longitudinal follow-up of established birth cohorts as they enter puberty and studies of cohorts of young men will allow us to relate early occurrence of TDS disorders as well as hormone levels, testis size, and chemical exposures to reproductive health in adolescence and adulthood. Associations between exposures, lifestyle, and health outcomes observed in the human studies will be explored mechanistically in animal and in vitro models.

Metabolomics and associated chemical mixture analysis will provide new insights into "real-life" human exposures and interaction with the endocrine systems. Systems biology and bioinformatic analytical approaches will be used for assessing exposure—outcome associations.

Results

Analyses of 121 chemicals in breast milk revealed distinctly different exposure to endocrine disrupters in Denmark and Finland. Danish children have higher exposure levels to most endocrine disrupters.

Dibutylphthalate (DBP) was found to prevent Leydig cell growth and testosterone secretion in fetal rat testis in vivo, explaining its phenotypic effects. Dexamethasone-induced intrauterine growth restriction enhanced the adverse effects of DBP treatment. In vitro exposure of fetal testes to monoethylhexyl phthalate caused disorganization of the morphology and decline in Leydig cell steroidogenesis.

Experimental studies on puberty highlighted the central role of the Kiss1 system in regulation of pubertal onset. This system is perturbed by endocrine disrupters in both male and female. The changes are linked to metabolic control of the body, determining susceptibility to obesity and diabetes.

The studies will add epidemiological and mechanistic information about reproductive and developmental effects of environmental contaminants, helping to identify connections between exposures, disrupted reproductive maturation and mis-programming of metabolic homeostasis.

Project Partners	
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