Extramural papers of the month

By Nancy Lamontagne

- Epigenetic effects of DDT lead to obesity in later generations
- Air pollution and psychological distress during pregnancy
- Eliminating damaged mitochondria from neuronal cells
- Maternal inhalation of nanomaterials can influence fetal health

Epigenetic effects of DDT lead to obesity in later generations

A mouse study, supported in part by NIEHS, indicates that ancestral exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) can promote obesity and associated disease in later generations. The findings imply that environmental exposures experienced several generations before might influence rates of obesity, although the degree of involvement is not known.

To examine potential transgenerational effects of DDT, the researchers transiently exposed pregnant female rats to DDT and then looked for obesity and obesity-related disease in the next three generations of offspring. The first generation offspring, which were directly exposed as fetuses, did not develop obesity, but did show kidney, prostate, ovary disease, and tumor development as adults. In the third generation or great-grand-offspring, more than 50 percent of males and females developed obesity. The transgenerational transmission of disease took place through both female (egg) and male (sperm) germlines. The researchers found differential DNA methylation regions, which are epigenetic changes in sperm, in the third generation. Genes associated with the identified differential DNA methylation regions were previously shown to be associated with obesity.

DDT was developed as a pesticide in the 1940s and was commonly used in the United States until banned in 1972. It is very persistent in the environment and still used to control malaria in other parts of the world. The researchers say that the long-term health and economic effects of DDT exposure on future generations should be considered in areas where DDT is used.


Air pollution and psychological distress during pregnancy

Research supported by NIEHS found that maternal psychological distress, combined with exposure to polycyclic aromatic hydrocarbon (PAH) air pollution during pregnancy, adversely affects children’s behavioral development. The results point to the need for a multifaceted approach for preventing developmental problems in children.

The researchers followed 248 children of nonsmoking white women in the coal-burning region of Krakow, Poland, from before birth until age 9. They used personal air monitoring during pregnancy to determine prenatal PAH exposure, and used the Psychiatric Epidemiology Research Instrument-Demoralization to determine maternal demoralization, a measure of psychological distress. The Child Behavior Checklist was used to evaluate child behavior.

The researchers found that maternal demoralization was linked with behavioral problems in the children, including anxiety, depression, attention problems, rule-breaking, externalizing problems, and aggressive behavior. The effects of demoralization were greatest among children with higher levels of prenatal exposure to PAHs.


Eliminating damaged mitochondria from neuronal cells

NIEHS-supported researchers have provided evidence that the externalization of the mitochondrial phospholipid cardiolipin signals for the elimination of damaged mitochondria in neuronal cells. Dysfunctioning mitochondria generate reactive oxygen species and release mediators that kill cells. So, recognizing and breaking down unhealthy mitochondria by autophagy, a process of metabolically mediated cell degradation, is essential for cellular health.
Cardiolipin is found in the inner membrane of healthy mitochondria and is not present in any other organelle. Using primary cortical neurons and neuroblastoma cells, the researchers found that the insecticide, rotenone; substances that destroy the dopaminergic and noradrenergic neurons, staurosporine and 6-hydroxydopamine; and other promitophagy stimuli caused cardiolipin to move from the inner mitochondrial membrane to the mitochondrial surface. If the scientists inhibited cardiolipin synthase, or a protein that transports cardiolipin to the outer mitochondrial membrane, delivery of mitochondria to autophagosomes decreased.

The researchers also found that the autophagy protein microtubule-associated-protein-1 light chain 3 (LC3) contains cardiolipin-binding sites important for the engulfment of mitochondria. LC3 mediates both autophagosome formation and cargo recognition.

The findings from this study point to a mechanism by which externalized cardiolipin, in injured mitochondria, interacts with LC3, mediating targeted autophagy of mitochondria in primary neurons and transformed neuronal cells.


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**Maternal inhalation of nanomaterials can influence fetal health**

NIEHS grantees report evidence that maternal inhalation of engineered nanomaterials can have fetal and maternal microvascular effects in an animal model. Microcirculation is important for fetal health, because it regulates blood flow distribution and protects downstream tissues from high arterial pressures and blood flow rates.

The researchers designed a study to evaluate the microvascular effects of maternal exposure to nanomaterials, and to find out if the Barker hypothesis applies at the microvascular level. The Barker hypothesis proposes that fetal development, within a hostile gestational environment, may predispose or program future sensitivity. The researchers placed pregnant rats in an inhalation chamber, where they were exposed to nanotitanium dioxide aerosols for five hours per day, for an average of 8.2 days.

Exposure to the engineered nanomaterials led to significant maternal and fetal microvascular dysfunction. Fetal microvessels, isolated from exposed dams, demonstrated significant impairments to signals of vasodilation specific to mechanistic signaling and shear stress. The maternal uterine microvascular reactivity was also affected. The researchers conclude that maternal inhalation of engineered nanomaterials can influence fetal health and that the Barker hypothesis does apply at the microvascular level.


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