

Report 94: Toxicants as potential metabolic disruptors

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Brief History: There is a high prevalence of obesity and diabetes.

The rapid change in this prevalence is consistent with an environmental etiology.

Some experimental and human evidence indicates toxicants may be a part of this environmental etiology.

Discussion Highlights:

Could toxicants help to explain why some obese persons are otherwise 'healthy' while others are diabetic, dyslipidemic, and/or insulin resistant?

Changes in childhood prevalence of obesity and type 2 diabetes are particularly striking. Basic science indicates metabolic programming occurs in the pre- and peri- natal period, and is modifiable by the environment. The toxicant environment is under-examined as a modifier of metabolic programming.

The pharmacokinetics of obesity complicates the dose response curve in individual potential target tissues of metabolic disruptors. Pharmacokinetics along with toxicant effects on lipid homeostasis also complicate epidemiologic analyses, particularly with respect to cross-sectional studies and to adjusting toxicants by blood lipid levels.

Physiologic mechanisms and/or causal partners of metabolic disruption may include maternal environment, epigenetics, stress, gut flora, inflammation, insulin action, as well as the quantity and quality of micro- and macro-nutrients. Multiple tissues, e.g. liver, muscle, adipose, CNS, and organelles, e.g. mitochondria and endoplasmic reticulum, may be the sites of these mechanisms.

Metabolic disruption may include diminished thriving and states of under nutrition. Consideration of this concept is of particularly relevance to global health.

Biomarkers of metabolic disruption are available for human studies-for instance one can conduct clinical studies with metabolic tracers in combination with exposure assessments.

Recommendations:

Consider the potential of metabolically dysfunctional states (e.g. obesity, insulin resistance, diabetes) as outcomes of toxicant exposures as well as toxicant effect modifiers/susceptibility factors.

Examine the role of early life exposure in metabolic disruption.

Conduct prospective human studies to test the metabolic disruption hypothesis.

Add a metabolic component to high throughput screens and reproductive toxicology tests already in place.

Foster interdisciplinary approaches to metabolic disruptor research through the inclusion of toxicologists, epidemiologists, endocrinologists, nutritionists, and microbiologists.

Leverage the NIDDK Mouse Metabolism Phenotyping Cores to conduct state of the art whole body animal studies.

Utilize metabolomics technologies to examine metabolic disruption.

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