Disruptores Metabólicos y Obesidad

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Recent “epidemics” of chronic diseases like diabetes and obesity are due to Gene-Environment Interactions over time

“Genotypes can only work in the presence of an environment, and environments have effects that are dependent on genotypes”

Speakman et al, 2012
Environment is everything but the genome

See Environment and Disease Risks by Rappaport and Smith, Science 330:460-461, 2010
An endocrine disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.

>100,000 chemicals in commerce

Some % are toxic to humans and wildlife

Some % are endocrine disruptors

Some % are obesogenic, diabetogenic or both
% of people tested by CDC
EPIDEMIOLOGICAL DATA LINKING EDCs
OBESITY AND/OR DIABETES
EDC-2: The Endocrine Society’s Second Scientific Statement on Endocrine-Disrupting Chemicals


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Important variables for the final phenotype

Exposure levels on humans
Dosage on animal models

Timing of Exposure

Gender and Age
We all carry a Chemical Body Burden

287 chemicals in cord blood

47 chemicals in every pregnant woman tested

In breast milk (BPA, PCBs, dioxins, pesticides, mercury, flame retardants)
Mode of action

**ADIPOCYTES**

- **AhR**
- **ERs**
- **PPARY**

Lipid metabolism
- Inflammation

Adipogenesis:
- + insulin resistance
- + IL-6
- + TNFα
- + INFγ

**β-CELLS**

- **ERs**
- **insulin**
- **AhR**
- **GLUT2**

Hyperinsulinaemia
Hypoinsulinaemia

**Diagram Elements**
- **BPA Xenoestrogens**
- **PCB Dioxins**
- **Insulin**
DNA methylation and histone modification


Gilbert and Epel, Sinauer, 2015
Understanding Epigenetic Effects of Endocrine Disrupting Chemicals: From Mechanisms to Novel Test Methods

**Diagram A:**
- DNA methylation:
  - DNMTs
  - NRs
  - TDG
  - BER
- 5mC
- 5hmC
- 5caC
- 5fc

**Diagram B:**
- EDC action
- Changes in activity or gene/protein levels
- Interaction
- Regulation

**Diagram C:**
- non-coding RNAs:
  - DNA
  - ncRNA
  - InRNA
  - Chromatin modifiers

**Diagram D:**
- Nuclear receptors (e.g., ER/AR)
- DNMTs
- TETs/TDG
- SAM/methyl donors
- Histone modification
- Histone modifiers
Figure 2 Potential mechanisms of obesogen action that alter metabolic set-points and increase the risk of obesity

Heindel, J. J. et al. (2015) Endocrine disruptors and obesity
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2015.163
Es = Ei - Eo

Es, rate of energy storage
Ei, rate of energy intake
Eo, rate of energy output
Adult mice

TCDD increase expression SGLT1 and GLUT2
Increase plasma glucose during GTT

Gut microbiota:
PCBs, Chlorpyrifos and Diazinon affect microbiota composition
TDCF increases short chain fatty acids
Alters hepatic lipogenesis, glycogenesis and gluconeogenesis
Ei, rate of energy intake

**Perinatal exposure in mice**

**Bisphenol-A and DES**
Alter expression of genes encoding:
- Estrogen Receptors
- NPY and AgRP (anorexigenic)
- POMC (orexigenic)
Increase POMC fibre density in the PVN

**TBBPA**, Decreases mRNA levels of MC4R and TSH-releasing hormone
**TBT** increases feeding
**TCDD and PFOS**, decrease food intake
Eo, rate of energy output
\[ E_{o} = E_{\text{thermogenesis}} + E_{\text{physical activity}} + E_{\text{BMR}} \]

**Perinatal exposure in mice**

**DDT**
Decrease energy expenditure without changes in physical activity
Decrease BAT expression of PGC-1alpha and Dio2 (Type 2 iodothyronine deiodinase)

**PFOA**, decreases body weight at birth and Increase BAT depots at 18 months offspring
Es, rate of energy storage

Heindel et al, Reproductive Toxicology 2017
TBT and Phthalates binds PPARγ
Bisphenol-A to ERs

BPA, PFOA in offspring increase leptin and decrease adiponectin serum levels
BPA increases release of IL-6 and TNF

Heindel et al, Reproductive Toxicology 2017
Perinatal Bisphenol-A treatment:
Increase lipogenesis via Srebp1c, Acc, Fasn (SREBP1, ACC, FAS)
Increase triglyceride accumulation, via Pparg, Prkag1, Cd36 and Acacb2 (PPARgamma, AMPK, CD36, ACC2)
Decreases glycolysis via Gck (GKC)

Heindel et al, Reproductive Toxicology 2017
\[ E_s = E_i - E_o \]
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Figure 1 Endocrine-disruptor-induced epigenetic transgenerational inheritance

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