Endocrine Disrupting Chemicals (EDCs) and the Obesity Epidemic

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Main Points

- Obesogens exist and contribute to obesity epidemic
- Obesogen action may involve reprogramming of stem cells
- Effects of obesogen exposure are heritable
Non-communicable Diseases On the Rise

- Leukemia, brain cancer: over 20% increase since 1975

- Asthma: doubled between 1980 and 1995, stays elevated

- Difficulty in conceiving and maintaining pregnancy: 40% more women in 2002 than in 1982 (doubled in women aged 18-25)

- Autism diagnosis: increased 1000% over the past 3 decades

- Obesity: Increased 3 fold in US over past 40 years doubled worldwide last 20 years

- Genetic changes cannot explain increases in these diseases!

- Account for 35 million deaths each year

- 60% of all deaths globally (80% occur in developing countries)
Why do Certain People Develop Disease While Others Remain Healthy?

- Genetics and SNPS
- Poor Nutrition
- Environmental Factors
- Other Diseases
- Stress
- Development and Age
- Drugs

Adverse Health Outcomes

Comorbidity Factors

- Role of environmental factors is important and under explored
The Worldwide Obesity Epidemic

- 34% of the US population are clinically obese (BMI > 30)
  - Double worldwide average (Flegal et al. JAMA 2010;303:235-241)

- 68% are overweight (BMI > 25) - 86% estimated by 2020

- Obesity accounts for a huge fraction of healthcare costs
  - $85.7 billion annually in US (2005), $147 billion (2009)
  - New model (J. Health Economics, 2012) - $209.7 billion in 2008
  - 20.6% of US healthcare costs.

- Obesity is associated with increases in
  - Metabolic syndrome -> type 2 diabetes
  - cardiovascular disease
  - hypertension
  - stroke
How does obesity occur?

- Prevailing wisdom - “couch potato syndrome”
  - Positive energy balance, i.e., too much food, too little exercise
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- **Prevailing wisdom** - “couch potato syndrome”
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- Are there other factors in obesity?
  - Stress (elevated glucocorticoids)
  - Inadequate sleep (stress?)
  - “Thrifty” genes which evolved to make the most of scarce calories
  - Viruses, gut microbes, SNPs

- What about role of prenatal nutrition or in utero experience?
  - Southampton studies
  - Maternal smoking decreases birth weight and increases obesity

- Is there a role for industrial chemicals in rise of obesity?
  - Baillie-Hamilton (2002) postulated a role for chemical toxins
  - Obesity epidemic roughly correlates with increased chemical use

- Many chemicals have effects on the endocrine system
Hormonal control of weight

- **Hormonal control of appetite and metabolism**
  - Leptin, adiponectin, ghrelin are key players
  - Leptin, adiponectin - adipocytes
  - Grehlin - stomach
  - Thyroid hormone/receptor
    - Sets basal metabolic rate

- **Hormonal control of fat cell development and lipid balance**
  - Regulated through nuclear hormone receptors RXR, PPARγ
  - PPARγ - master regulator of fat cell development
    - increased fat cell differentiation
    - Increased storage in existing cells
    - Increased insulin sensitivity

*From Nature Medicine 10, 355 - 361 (2004)*
Endocrine Disrupting Chemicals (EDCs) affect many organ systems

- **“Endocrine Disruptor” - an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”** - The Endocrine Society, 2012
  - Wrong signal, loss of signal, wrong place at wrong time
  - Hormones work at low concentrations and so do EDCs

- How are we exposed to EDCs?
  - persistent pollutants (POPs)
  - dietary components (pesticides)
  - personal care products
  - cleaning materials
  - food packaging

- Everyone is exposed
Do EDC-mediated disturbances in endocrine signaling pathways play a role in obesity?
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EDCs and the obesogen hypothesis

- **Obesogens** - chemicals that inappropriately stimulate adipogenesis and fat storage, disturb adipose tissue homeostasis, or alter control of appetite/satiety to lead to weight gain and obesity

- Pre- and postnatal exposure to EDCs such as environmental estrogens (ER) increases weight
  - DES, genistein, bisphenol A
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- Thiazolidinedione anti-diabetic drugs (PPARγ)
  - Increase fat storage and fat cell number at all ages in humans

- Urinary phthalates correlate with waist diameter and insulin resistance in humans
  - Many chemicals linked with obesity in epidemiological studies

- Several compounds cause adipocyte differentiation in vitro (PPARγ)
  - Phthalates, BPA, alkylphenols, PFOA, organotins

- Existence of obesogens is plausible
Endocrine disruption by organotins

- Organotins -> imposex in mollusks

- Sex reverses genetically female flounder and zebrafish -> males

- Which hormone receptors might be organotin targets?

- We found that tributyltin (TBT)
  - Binds and activates at ppb (low nM) two nuclear receptors, RXR and PPARγ critical for adipogenesis
  - TBT induced adipogenesis in cell culture models (nM)
  - Prenatal TBT exposure led to weight gain in mice, in vivo

Grun et al., Molec Endocrinol, 2006
TBT increases testis fat pad weight at 10 weeks

Fat depot size increases at the expense of overall body mass

Grun et al., Molec Endocrinol, 2006
How does TBT exposure cause weight gain?

- Changes in the hormonal control of appetite and satiety?
- Altered ability of adipocytes to process and store lipids?
- Increased number of adipocytes or pre-adipocytes?
- Mesenchymal stem cells (MSCs) (a.k.a. multipotent stromal cells) precursors to many lineages including bone, cartilage, and adipose.
  - MSCs differentiate into adipocytes following rosiglitazone exposure
  - MSCs may (or may not) home to adipose depots after induction
- **Hypothesis:** TBT induces adipogenesis in MSCs
MSCs can give rise to many cell types in vivo

- PPAR\(\gamma\) controls choice between fat and bone pathways
- Expression and activation of PPAR\(\gamma\) favors the fat and inhibits bone formation.

Takada et al., 2009 Nature Reviews Immunology 5, 442-447

Kirchner et al., 2010 Molecular Endocrinology 24, 526-539
Prenatal TBT exposure reprograms MSCs to become fat cells instead of bone cells

Kirchner et al, 2010 Molecular Endocrinology 24, 526-539
Are effects of TBT exposure heritable?

8 weeks old
- Body weight
- Adipose tissue weight
- Adipocyte size
- MSC gene expression profile
- Liver adiposity
- Hepatic gene expression

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

**Heavier fat depots**

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**Epididymal WAT**

- **Vehicle**
- **ROSI**
- **TBT 5.4 nM**
- **TBT 54.2 nM**
- **TBT 542 nM**

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**Peri-renal WAT**

- **Vehicle**
- **ROSI**
- **TBT 5.4 nM**
- **TBT 54.2 nM**
- **TBT 542 nM**

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**Interscapular WAT**

- **Vehicle**
- **ROSI**
- **TBT 5.4 nM**
- **TBT 54.2 nM**
- **TBT 542 nM**

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Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

*Non-alcoholic fatty liver disease*

<table>
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<th>DMSO</th>
<th>ROSI</th>
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<td></td>
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Chamorro-Garcia et al., Environ Health Perspect, 2013
Obesogen exposure and development

- Organotins are exceptionally potent agonists of RXR and PPAR_γ at environmentally-relevant levels (ppb)

- TBT drives adipocyte differentiation in cell culture

- TBT exposure during development induces adipogenesis in many vertebrates
  - Mouse, rats, frogs, fish
  - Inhibits bone formation in culture and in females

- Maternal TBT exposure causes transgenerational effects

- TBT detected in people at levels that cause effects in animals

Is the environment making us fat?
### Obesogens - Just the Tip of the Iceberg?

<table>
<thead>
<tr>
<th>TBT/TPT</th>
<th>DES</th>
<th>Nicotine</th>
<th>fructose</th>
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<tr>
<td>Phthalates</td>
<td>Bisphenol A</td>
<td>Air pollution</td>
<td>COX2 inhibitors</td>
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<td>PFOA</td>
<td>Genistein</td>
<td>BaP</td>
<td>PCBs ?, PBDEs ?</td>
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**Organophosphate pesticides**

**many fungicides**

- What don’t we know yet?
  - How many obesogens are out there
  - Body burdens in population
  - Molecular targets of action beyond RXR-PPARγ
  - Critical windows of exposure
  - How does prenatal exposure alter adult phenotype?
  - Is the prenatal reprogramming epigenetic?
Implications For Human Health

• Diet and exercise are insufficient to explain obesity epidemic particularly in the very young

• Obesogens inappropriately stimulate adipogenesis and fat storage
  - Prescription drugs
    • Thiazolidinedione anti-diabetic drugs (Actos, Avandia)
    • Atypical antipsychotics, anti-depressants
  - Environmental contaminants
    • organotins, estrogens (BPA, DEHP), PFOA/S, DDE, POPs
    • Many fungicides, organophosphates, parabens

• Prenatal obesogen exposure reprograms exposed animals to be fat
  - Epigenetic changes alter fate of stem cell compartment -> more preadipocytes and more adipocyte progenitors
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• Obesogens shift paradigm from treatment to prevention during pregnancy, childhood and puberty
  - Reduced exposure to obesogens, optimized nutrition
An better paradigm for chronic diseases?

Comorbidity Factors

- Poor Nutrition
- Other Diseases
- Stress
- Development and Age
- Drugs
- Environmental Influences

Genetics and SNPS

Adverse Health Outcome

Comorbidity Factors
Chemicals with Transgenerational Effects

- Tributyl tin (RXR, PPARγ) plastic, industrial use, water pipes) - increased fat mass, reprogram stem cells to produce more fat cells over time, fatty liver disease (Chamorro-Garcia et al, 2013)

- Vinclozolin (anti-androgen) - fungicide, impairs male reproductive function (Anway and Skinner, 2005)

- Plastics mixture, BPA, DEHP, DBP, (estrogen, anti-androgen) obesity, reproductive diseases, sperm epimutations (Manikkam et al, 2013)

- Hydrocarbons, JP-8 jet fuel (?) obesity, reproductive diseases, sperm epimutations (Tracey et al, 2013)

- BPA, estrogen (plastics, thermal paper, recycled paper, food packaging), altered social interactions, modified gene expression (Wolstenholme et al, 2012)

- DDT, estrogen (pesticide) - 50% of F3 males and female rats develop obesity (Skinner et al, 2013)
Chemicals with Transgenerational Effects

- Existence of transgenerational effects raises the stakes in the argument about whether and what chemicals to regulate.

- What will be the cost of waiting for conclusive evidence of harm in humans before acting?
Testing for effects of chemical exposure
• UCI - Blumberg Lab
  Kotaro Azuma
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  Riann Egusquiza
  Catrine Ibrahim
  Amanda Janesick
  Takashige Kawakami
  Ron Leavitt
  Eric Martinez
  Mary Sargious
  Bassem Shoucri
  Weiyi Tang
  Griselda Valdez

• Former lab members
  Christy Boulos
  Giorgio Dimastrogiovanni
  Felix Grun
  Elina Karimullina
  Séverine Kirchner
  Heidi Käch
  Jasmine Li
  Lenka Vanek

• NINS - Okazaki, Japan
  Taisen Iguchi

• NIHS - Tokyo, Japan
  Jun Kanno

• Uppsala University
  Monica & Lars Lind

• MGH/Harvard Medical School
  Toshi Shioda

Funding from NIEHS, US-EPA, UC TSR&TP