Endocrine Disrupters as Obesogens

Is the environment making us fat?

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The Worldwide Obesity Epidemic

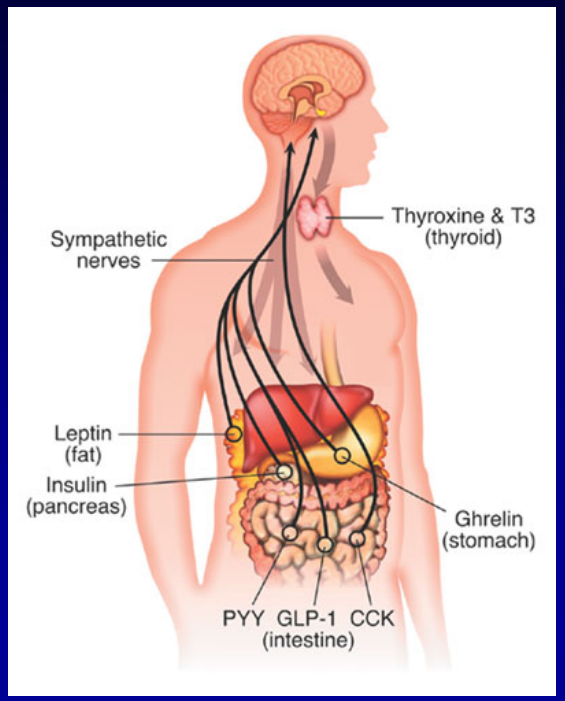
- 60 million people in the US are clinically obese
  - >30% above “ideal” body weight
- Obesity accounts for 8% of healthcare costs in Western countries
  - $75 billion annually in US (2005)
- Obesity is associated with “metabolic syndrome” -> type 2 diabetes and cardiovascular disease
  - Central (abdominal obesity)
  - Atherogenic dyslipidemia (high triglycerides, high LDL, low HDL)
  - Hypertension
  - Insulin resistance
  - Prothrombotic state
  - Pro-inflammatory state (elevated CRP)

How does obesity occur ?

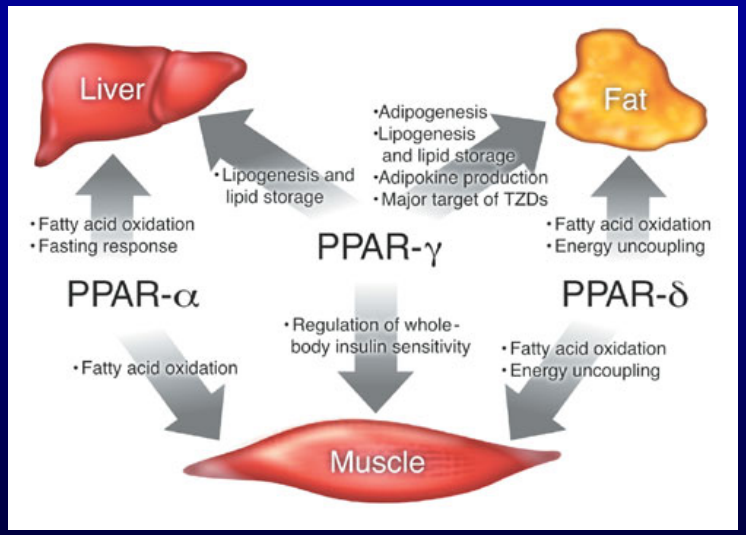
- Prevailing wisdom – "couch potato syndrome"
  - Positive energy balance, i.e., too much food, too little exercise
- Other factors ?
  - Stress (elevated glucocorticoids)
  - Inadequate sleep (stress?)
  - "Thrifty" genes which evolved to make the most of scarce calories
  - Viruses, SNPs
- What about role of prenatal nutrition or in utero experience?
  - Maternal smoking decreases birth weight and increases obesity
- What about the role of industrial chemicals in rise of obesity?
  - Baillie-Hamilton (2002) postulated a role for chemical toxins
  - obesity epidemic roughly correlates with a marked increase in the use of chemicals (plastics, pesticides, etc.)
- Many chemicals have effects on the endocrine system

Hormonal control of weight

- Hormonal control of appetite and metabolism
  - Leptin, resistin adiponectin ghrelin are key players
    - Leptin, adiponectin, resistin – 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 fat storage in existing cells
    - Increased insulin sensitivity



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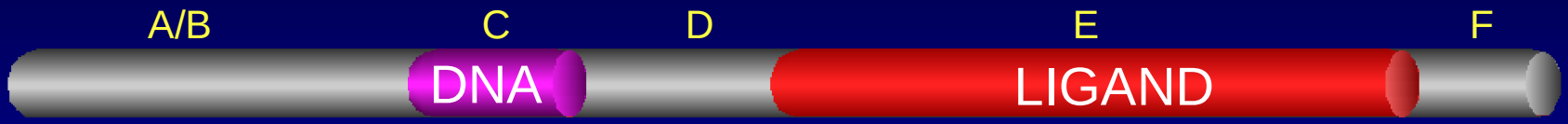
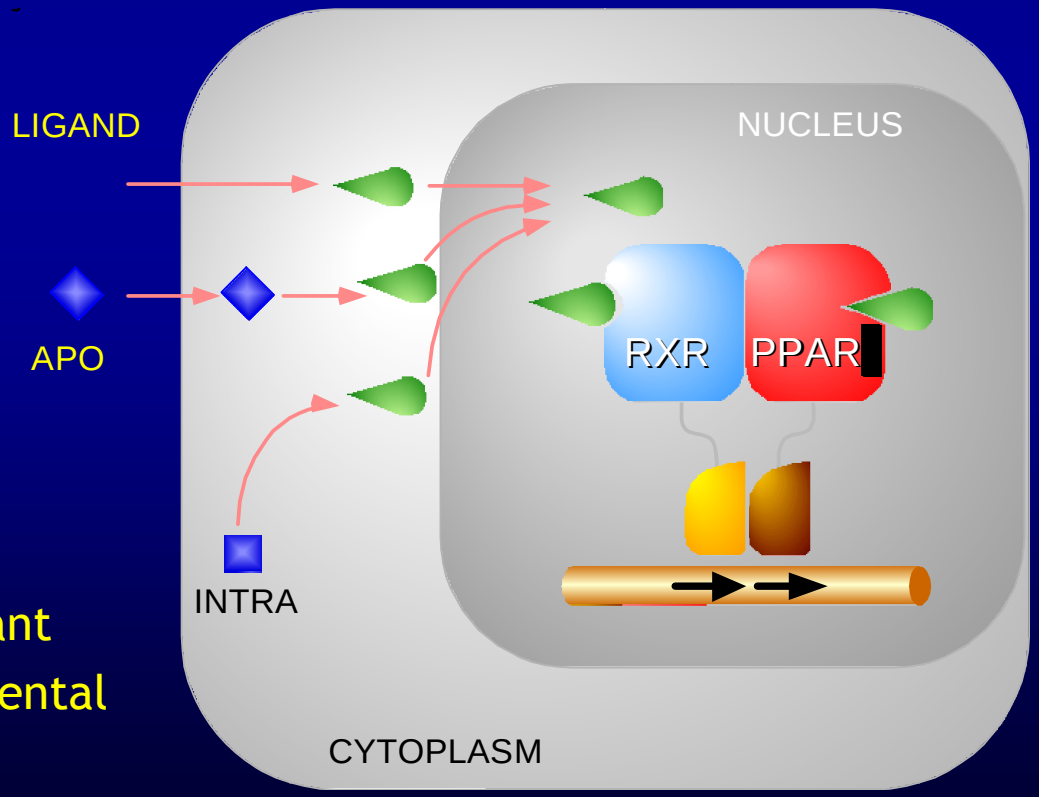
Nuclear Receptors - A Large Family of Ligand Modulated Transcription Factors



- Bind to specific DNA targets - Hormone Response Elements
  - Most are activators
  - Some constitutive
  - Few inactivate
- Ligands are small lipophilic molecules that freely enter cells
  - Diffuse from source & penetrate to a target
- Respond to low levels of hormone
  - Parts per billion levels
  - Regulation of levels is important
  - Can be disrupted by environmental contaminants



Endocrine Disrupting Chemicals (EDCs)

- *Endocrine disrupter* - a compound that mimics or blocks the action of endocrine hormones, either directly or indirectly

- Often persistent pollutants or dietary components

- Disturb development, physiology and homeostasis

- Frequently act through nuclear hormone receptors
  - Environmental estrogens
  - Anti-androgens
  - Anti-thyroid

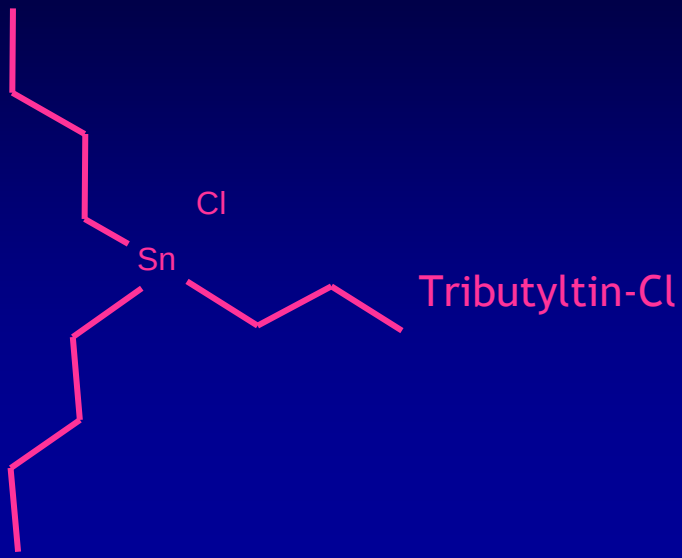
- Are disturbances in endocrine signaling pathways involved in adipogenesis and obesity ?

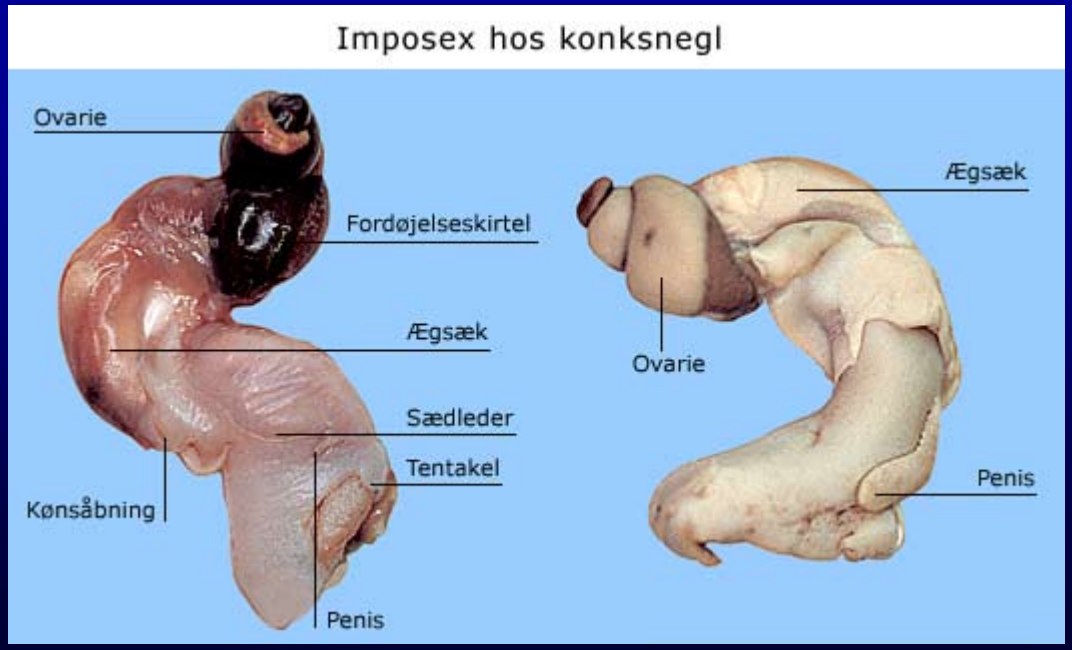
The Obesogen Hypothesis

- *Obesogens* - chemicals that inappropriately stimulate adipogenesis and fat storage, exist and contribute to obesity epidemic
- Pre- and postnatal exposure to environmental estrogens (ER) increases weight
  - DES, genistein
- Thiazolidinedione anti-diabetic drugs (PPARγ)
  - Increase fat storage and fat cell size at all ages in humans
  - Reduce insulin resistance in muscle but increases obesity which exacerbates diabetes
- Several compounds cause adipocyte differentiation in vitro (PPARγ)
  - Organotins, phthalates, BPA, PFOA, alkylphenols,
- Urinary phthalates correlate with waist diameter and insulin resistance in humans

Endocrine disruption by organotins

- Tributyltin -> causes imposex in molluscs
  - Imposition of male sex characteristics on female mollusks
- Impairs shell development in bivalve mollusks
- Sex reverses fishes (genetically female flounder and zebrafish -> males)





How do organotins cause endocrine disruption?

- How do organotins cause sex-reversal in mollusks and fishes?
  - Direct inhibition of aromatase (CYP19) activity (μM concentrations)
  - Inhibition of testosterone storage

- Transcriptional effects on aromatase expression
  - CYP19 in human ovarian granulosa cells is sensitive to inhibition by TBT, RXR- and PPARγ-specific ligands

- TBT alters sex determination – typically female -> male
  - TBT effects are seen at nM doses and below
  - Sex determination requires sex steroids at critical times
  - Sex steroids act through nuclear receptors

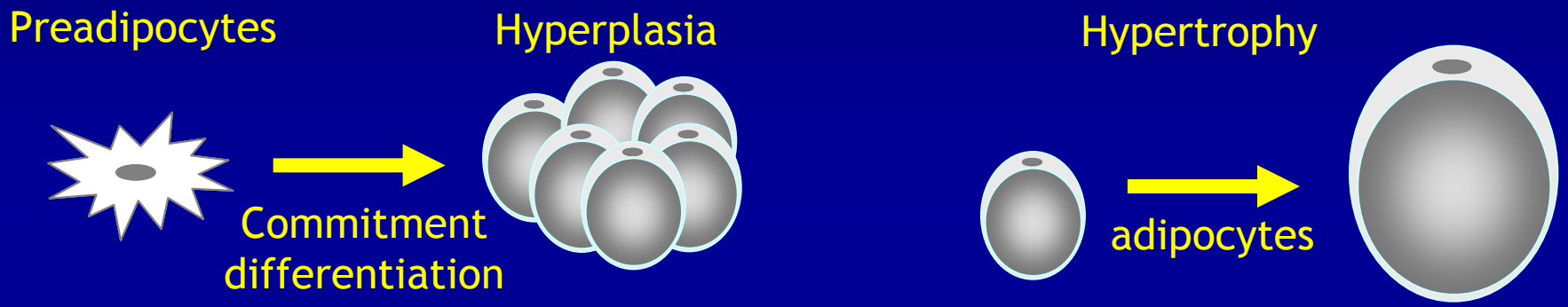
- *Hypothesis – TBT alters the activity of one or more nuclear receptors, thereby causing endocrine disruption*
  - Test nuclear receptors for activation or inhibition by organotins
  - Expect effect on steroid receptor activity

What is the effect of TBT on hormone receptors?

- TBT did not affect activity of sex steroid receptors at all
- TBT binds to and activates RXR-PPARγ with high affinity
  - TBT exposure causes RXR-PPARγ target genes to be expressed
  - Activation of RXR-PPARγ converts susceptible cultured cells into fat cells
- Prenatal TBT exposure predisposes animals to become obese
  - Exposed animals were about 15% heavier despite normal diet and exercise
  - Metabolism has been altered

How does TBT exposure cause weight gain?

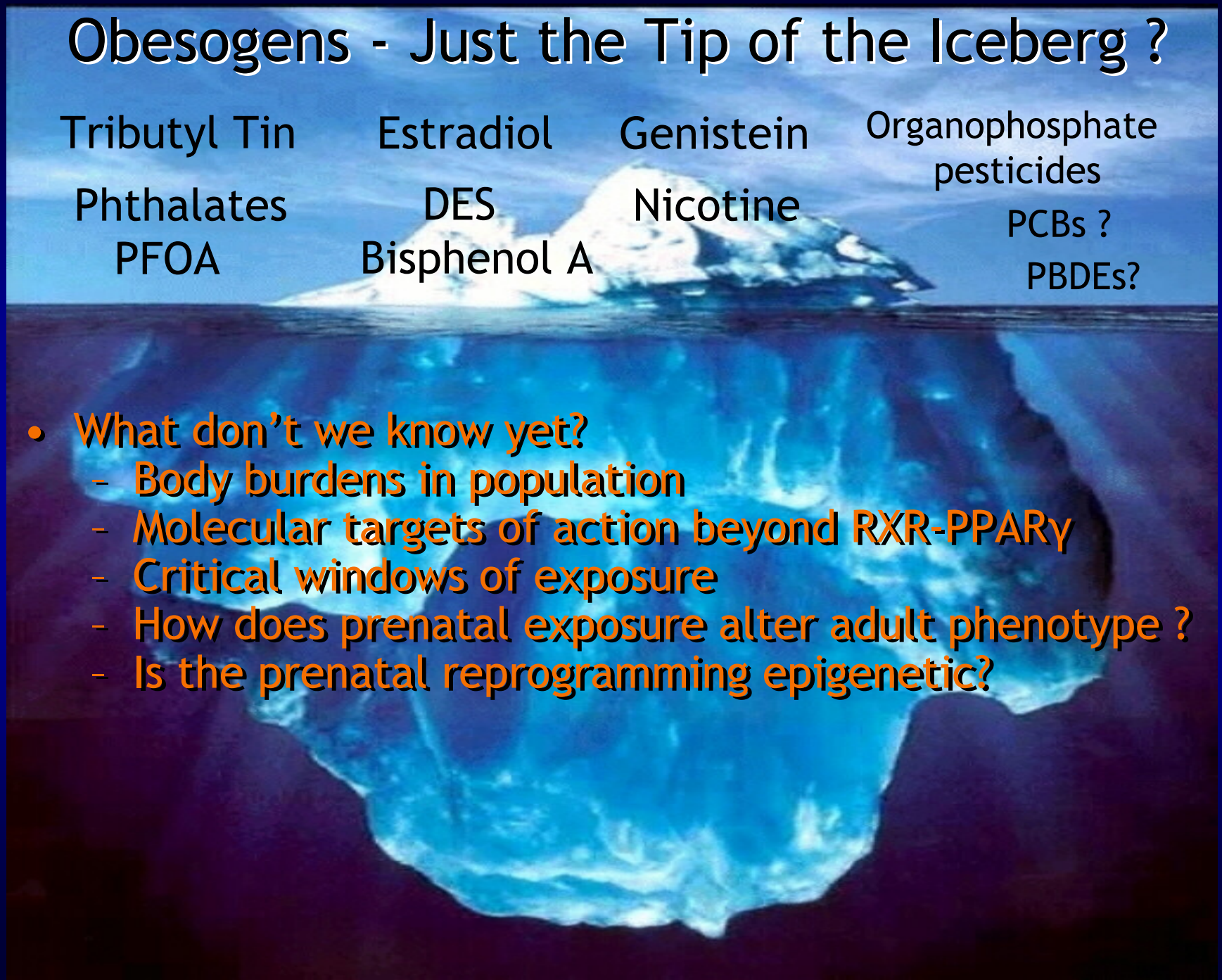
- Changes in the hormonal control of appetite and satiety?
- Altered ability of adipocytes to process and store lipids?
- Increased number of adipocytes or pre-adipocytes?



- Mesenchymal stem cells (MSCs) (now called 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

- TBT induces cultured MSCs to become adipocytes
  - Effects of TBT on human obesity likely to be via MSCs

Obesogens - Just the Tip of the Iceberg ?



- What don't we know yet?
  - 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?

Take Home Messages

- Diet and exercise are insufficient to explain obesity epidemic
- Obesogens inappropriately stimulate adipogenesis and fat storage
  - Environmental contaminants
    - TBT, environmental estrogens (BPA, DEHP), PFOA
  - Prescription drugs
    - Thiazolidinedione anti-diabetic drugs (Actos, Avandia)
    - Atypical antipsychotics (olanzapine)
    - Anti-depressants (tricyclics, SSRIs)
- Prenatal obesogen exposure reprograms the metabolism of exposed animals, predisposing them to obesity.
  - Likely to be epigenetic
- Obesogen exposure targets multiple cellular pathways, some of which involve nuclear receptors.