The Role of Polychlorinated Biphenyls in the Development of Diabetes

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Dr. Karen Wetterhahn Memorial Award

- Professor of Chemistry at Dartmouth College
- Cofounded Dartmouth’s Women in Science Project
- Program Director of Dartmouth College Superfund Research Program
Dr. Karen Wetterhahn Memorial Award

- Dr. Courtney Kozul-Horvath, 2010 Wetterhahn Award Recipient
- Post-doctoral fellow at Dartmouth College studying the immunological effects of arsenic exposure during pregnancy in mice
Outline

- Polychlorinated biphenyl (PCB) background
- Coplanar PCBs induce diabetes in lean mice
- PCBs in obesity/weight loss model
Superfund Research Program at the University of Kentucky
Superfund Research Program at the University of Kentucky

- **Administrative Core**
  - Inflammation
  - **Biomedical Projects**
    - [1] Atherosclerosis
    - [2] Perinatal impacts
    - [3] Diabetes
  - Chlorinated Organics
  - Oxidative Mechanisms
  - Nutritional Agents

- **Research Translation Core**
  - Training
  - **Non-Biomed Projects**
    - [4] Sensing/Capture
    - [5] Remediation
  - Green Nanotechnologies

- **Research Support Core**

- **Community Engagement Core**

- **Chemical Structure**
  - Polychlorinated Biphenyl (PCB)

- Images of fruits and vegetables, and a glucose meter with a reading of 6.1.
PCBs: where do they come from?
PCBs: where do they come from?

Humans are harmed by intake through food, water, and air. Babies are harmed from mothers’ blood and breast milk.
Aryl hydrocarbon receptor (AhR)

- Evolutionally conserved cytosolic transcription factor.
- Endogenous ligands: derivatives of tryptophan, bilirubin, carotinoids, flavonoids, possibly fatty acids.
- Exogenous ligands: planar halogenated aromatic hydrocarbons and polycyclic aromatic hydrocarbons.

Mechanisms of action for PCBs via AhR
Diabetes prevalence

Disease characterized by high plasma glucose, either because the body does not produce enough insulin, or because cells do not respond to insulin that is produced.
KEY ORGANS OF DIABETES

- **PANCREAS**: decreased insulin secretion
- **KIDNEYS**: increased glucose reabsorption
- **Islet-α cell**: increased glucagon secretion
- **BRAIN**: neurotransmitter dysfunction
- **MUSCLE**: decreased glucose uptake
- **LIVER**: increased hepatic glucose production and decreased hepatic glucose uptake
- **ADIPOSE TISSUE**: increased lipolysis
- **DIGESTIVE SYSTEM**: decreased incretin effect
Exposure to POPs correlates to the incidence of type 2 diabetes

PCB77 induces expression of proinflammatory cytokines in adipose tissue

The working hypothesis of these studies is that exposure of lean mice to PCB77 induces diabetes by stimulating production of adipose TNF-α.
Does PCB77 result in dose-dependent glucose and insulin intolerance?

Male C57BL/6, Low Fat Diet

Vehicle
- PCB77 (2.5 mg/kg)
- PCB77 (50 mg/kg)
- PCB77 (248 mg/kg)

Week:
- Oral Gavage
- Animals Sacrificed

Weeks:
- 1
- 2
- Weeks 1 & 2
- Week 2

Prior to sacrifice:
- Glucose Tolerance Test
- Insulin Tolerance Test
PCB77-induced impairment of glucose and insulin tolerance is dose-dependent

PCB126-INDUCED IMPAIRMENT OF GLUCOSE AND INSULIN TOLERANCE IS DOSE-DEPENDENT

Is PCB77-induced impairment of glucose and insulin tolerance AhR-dependent?

- CH223191, a potent AhR antagonist
- Mice gavaged with CH223191 (10 mg/kg/day, oil) for 1 week prior to and for duration of study

**Experimental Design**

<table>
<thead>
<tr>
<th>Male C57BL/6, Low Fat Diet</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td></td>
<td>CH223191</td>
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<tr>
<td></td>
<td>PCB77 (50 mg/kg)</td>
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<td>PCB77 + CH223191</td>
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<table>
<thead>
<tr>
<th>Week:</th>
<th>0 1 2</th>
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<tr>
<td>Gavage CH223191</td>
<td>Week 0, 1, 2</td>
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<tr>
<td>Gavage PCB77</td>
<td>Weeks 1 &amp; 2</td>
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<tr>
<td>Animals Sacrificed</td>
<td>Week 2</td>
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Is PCB77-induced impairment of glucose and insulin tolerance AhR-dependent?

Is PCB77-induced impairment of glucose homeostasis sustained?

Male C57BL/6,
Low Fat Diet

Vehicle

PCB77 (50 mg/kg)

Week: 1 2 3 4 5 6 7 8 9 10 11 12

Oral Gavage
Weeks 1 & 2

Animals Sacrificed
Week 2
Week 4

Monthly:
Glucose Tolerance Test
Insulin Tolerance Test

Week 2
Week 4
Week 12
PCB77 promotes sustained glucose and insulin intolerance

PCB77 accumulates in adipose tissue

PCB77 causes an adipose-specific increase in TNF-α in lean mice

Studies in Obese Mice - Hypothesis

With obesity, PCB77-induced diabetes is mitigated due to sequestration in lipid pools of adipose tissue. During weight loss, release of stored PCB77 from adipose tissue will blunt the beneficial effects of weight loss on glucose and insulin homeostasis.
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With obesity, PCB77-induced diabetes is mitigated due to sequestration in lipid pools of adipose tissue. During weight loss, release of stored PCB77 from adipose tissue will blunt the beneficial effects of weight loss on glucose and insulin homeostasis.

What does PCB77 do to glucose homeostasis during weight gain versus weight loss?

Groups:
- Male C57BL/6

High fat diet:
- 60% kcal from fat
- Fat sources: Lard > soybean oil
- Energy: 5.24 kcal/g

Vehicle

PCB77 (50 mg/kg)

Measurements:
- Monthly:
  - Glucose Tolerance Test
  - Insulin Tolerance Test

Weeks:
- Oral Gavage: Weeks 1 & 2
- Start LF Diet: Weeks 9 & 10
- Animals Sacrificed: Week 12

Animals Sacrificed:
- Week 12
- Week 16
What does PCB77 do to glucose homeostasis during weight gain *versus* weight loss?

**Groups:**
- Male C57BL/6

**High fat diet**
- 60% kcal from fat
- Fat sources: Lard > soybean oil
- Energy: 5.24 kcal/g

**Vehicle**

**PCB77 (50 mg/kg)**

**Measurements:**
- Glucose Tolerance Test
- Insulin Tolerance Test

**Weight Gain Phase**

- **Oral Gavage**
  - Weeks 1 & 2
  - Weeks 9 & 10

- **Start LF Diet**
  - Week 12

- **Animals Sacrificed**
  - Week 12
  - Week 16
What does PCB77 do to glucose homeostasis during weight gain *versus* weight loss?

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**Measurements:**
- Monthly:
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  - Insulin Tolerance Test

**Weight Gain Phase**
- Oral Gavage: Weeks 1 & 2
- Start LF Diet: Weeks 9 & 10
- Animals Sacrificed: Week 12

**Weight Loss Phase**
- Animals Sacrificed: Weeks 12 & 16

**Vehicle**

**PCB77 (50 mg/kg)**
PCB77-induced glucose intolerance is blunted in obese mice, but appears following weight loss.

**Glucose Tolerance**

**Insulin Tolerance**

PCB77-induced glucose intolerance is blunted in obese mice, but appears following weight loss.

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Supplemental Figure 6

PCB77 induces CYP1A1 and TNF-α mRNA abundance via the AhR in 3T3-L1 adipocytes

PCB77 induces CYP1A1 and TNF-α mRNA abundance via the AhR in 3T3-L1 adipocytes

A proposed adipocyte-specific mechanism for PCB-induced insulin resistance
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Adipocyte

Blood

Weight Loss

AHR
A proposed adipocyte-specific mechanism for PCB-induced insulin resistance

- Adipocyte
- Blood
- Weight Loss
- Oxidative Stress
- TNFα
- Insulin Resistance
- Glucose Intolerance
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