Gut Reactions: Can gut microbial and environmental chemical interactions contribute to the obesity and diabetes epidemic?

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Overview

• Global rates of obesity and Type II diabetes have increased dramatically

• Multiple environmental factors may contribute to these diseases:
  – Gut microbes, especially in the colon
  – Environmental chemicals (called obesogens and diabetogens)

• Studies suggest that person to person variation in the “gut microbiome” affects the toxicity / metabolism of many pharmaceuticals

• The majority of the environmental chemicals identified as “obesogens” or “diabetogens” also may be metabolized by gut microbes
Overview

• Interindividual variation in gut microbes may affect the absorption, distribution, metabolism, and excretion (ADME) of these chemicals.
• Therefore, we propose that this interindividual variation in gut microbes may affect the body burden of obesogenic and/or diabetogenic chemicals.
• SO, whether environmental chemicals affect obesity or diabetes may depend on your “gut reactions”.
Global rates of obesity and diabetes

The Obesity and Diabetes Epidemics

– U.S. obesity rates rose from 14.5% to > 33% over in the last three decades (Flegal 1998, Flegal 2010)

– Body Mass Index (BMI) and diabetes incidence have risen in many areas world-wide (Finucane 2011, Danaei 2011)

– Environmental factors may be important contributors to both of these diseases
The numbers

– The human “microbiome” has 3.3 million genes and 99% are of bacterial origin (Quin 2010)
– This is 150 times BIGGER than the human genome
– While many microbial species are shared, there is much variation in the microbial genes found between individuals (“interindividual” variation)
– Surprising, we know very little about the function of the microbiome
Gut microbes and obesity

– Studies of lean and obese twins suggested a “core” microbiome (Turnbaugh, 2009, and 2009a)

– A different study did not see specific microbial populations associated with obesity (Arumugam 2011)

– A study of intestinal by-pass patients suggested changes in obesity may affect gut ecology (Bjorneklett 1981)

– Studies in germ-free animals suggested a possible role of gut ecology in obesity (Backhed 2007, Fleissner 2010)
Gut microbes and obesity

• The role of microbes may include influencing:
  – Energy extraction (Turnbaugh 2006)
  – Fat storage regulation (Backhed 2004)
  – Endotoxemia-induced inflammation (Cani 2007, Cani 2008)
  – Dietary interactions (Backhed 2007, Fleissner 2010)
  – Satiety factors (Cani 2009, Ravussin 2011, Sanz 2010)
  – Immune function (Vijay-Kumar 2010)

• Ratios of microbial families
  – Some, but not all studies in obese and lean humans have found differences in the ratios of Bacteroidetes to Firmicutes (Ley 2006, Armougom 2009)
Gut microbes and diabetes

• Bariatric surgery patients show dramatic changes in gut ecology (Furet 2010) as well as glycemic control (Ahima 2011, Meijer 2011)

• Antibiotic treated mice obese (ob/ob) mice have improved glucose tolerance (Membrez 2008)

• Type I diabetes – few studies done to date
  – Certain bacterial toxins can damage pancreatic cells (Streptomyces toxin, bafilomycin A1, Myers 2003).
Environmental Chemicals

- **Obesogens** can affect the delicate balance of controls in lipid metabolism, fat generation, and energy balance (see pg. 14-17 of review)
  - Tributyl tin is a developmental obesogen in animal studies; little information on current human exposures
  - PFOA, emerging evidence as developmental obesogen
  - DES, nonylphenol, and genestein (estrogenic compounds) show some evidence of affecting adipose or insulin pathways, often at low doses
  - Bisphenol A shows mixed evidence as an obesogen in rodent studies and weak evidence in human studies
Environmental Chemicals

• **Diabetogens** (see pgs. 13-14 of the review)
  – Arsenic is a known diabetogen (global associations)
  – PCBs, DDE, dioxins, chlordane, HCB, brominated flame retardants, and variety of other pesticides used in agriculture, have been associated with higher incidences of Type II diabetes in human epidemiological studies
  – PFOA (perfluorooctanoic acid) shows mixed evidence for diabetes risk in large-scale human studies (Ludin 2009, MacNeil 2009)
Disposition of Environmental Chemicals

• Microbial affects on Absorption, Distribution, Metabolism and Excretion (ADME)
  – Change pollutant bioavailability
  – Direct “activation”
  – Production of endogenous toxins
  – Alter expression of host detoxification proteins
  – Change enterohepatic cycling
Disposition of Environmental Chemicals

• Changes in bioavailability
  – Leaky gut
    • Different microbes have different affects on permeability
  – Change in chemical form
    • Microbes can convert insoluble forms to bioavailable and bioactive forms (e.g. arsenic)
Disposition of Environmental Chemicals

• Direct activation by gut microbes
  – Gut microbes can convert PolyAromatic Hydrocarbons (PAHs) into estrogenic metabolites

Van de Wiele 2005
Disposition of Environmental Chemicals

- Changes in host detoxification enzymes

Claus et al. 2011
Disposition of Environmental Chemicals

- Production of endogenous toxins
  - Normal amino acids may be “activated” by certain gut microbes
  - This can rob the host of important detoxification capacity

Clayton et al. 2009
Disposition of Environmental Chemicals

Altered Enterohepatic Cycling

- Ingestion followed by absorption in the small intestine
- Transport to the liver for 1st pass metabolism
- Metabolites secreted into the bile
- Metabolites reabsorbed from intestines or excreted.
  - e.g. Flame Retardants (Meijer 2006)

http://www.biology-online.org/
Gut Reactions can Produce Toxicants

- The cancer prodrug CPT-11 is activated by the liver to SN-38.
- SN-38 kills tumors, but is glucuronidated (SN-38G) and excreted.
- Gut microbes cleave the sugar from SN38G, producing SN38 which is toxic to gut epithelia.

Patel and Kaufmann 2010
Disposition of Environmental Chemicals

Interindividual variability in glucuronidase activity

Figure. β-Glucuronidase activity in fresh human faeces. Each sample of faeces was diluted with the anaerobic diluent and its activity was assayed with p-nitrophenyl glucuronide (□) and phenolphthalein glucuronide (□). Numbers against subjects indicate that samples were collected from the same subjects on different days.
## Chemicals that undergo Enterohepatic Circulation & Phase II metabolism*

<table>
<thead>
<tr>
<th>Non-Pesticide POPs</th>
<th>Pesticides</th>
<th>Metals</th>
<th>Other Chemicals</th>
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<tbody>
<tr>
<td>Polybrominated flame retardants</td>
<td>Alachlor</td>
<td>Arsenic</td>
<td>Bisphenol A*</td>
</tr>
<tr>
<td>PCBs*</td>
<td>Aldrin*</td>
<td>Cadmium</td>
<td>DES*</td>
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<tr>
<td>Dibenzo-dioxins*</td>
<td>Amitraz*</td>
<td>Mercury</td>
<td>Genestein*</td>
</tr>
<tr>
<td>Dibenzo-furans*</td>
<td>Chlorpyrifos*</td>
<td>Tributyl tin</td>
<td>Nonylphenol*</td>
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<tr>
<td></td>
<td>DDD, DDE, DDT*</td>
<td>Octylphenol*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dieldrin*, Endrin*</td>
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<td>Some Phthalates*</td>
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<tr>
<td></td>
<td>Heptachlor*</td>
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<tr>
<td></td>
<td>Hexachlorobenzene*</td>
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<tr>
<td></td>
<td>HCH, gamma &amp; beta*</td>
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<td></td>
<td>Trichlorofon*</td>
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* Indicates chemicals that are glucuronide Phase II conjugates.

Data extracted from Supplemental Table 1 in Snedeker and Hay’s 2011 EHP review article, [http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.1104204#Supplemental%20Material](http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.1104204#Supplemental%20Material)
Conclusions

• The potential exists for gut microbes to affect the disposition of many obesogenic and diabetogenic environmental chemicals

• We know almost nothing about the interindividual variation of gut microbes

• Understanding and controlling gut microbes will be key to combating obesity and diabetes
Talk based on our review:

Do Interactions Between Gut Ecology and Environmental Chemicals Contribute to Obesity and Diabetes?

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http://dx.doi.org/10.1289/ehp.1104204

Includes a Supplemental Table on the “Phase II metabolism of obesogenic and diabetogenic chemicals.” Table can be accessed at:

http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.1104204#Supplemental%20Material
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