Genetic Models of Obesity in Adults: Impact on Cardiovascular Function

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Obesity Trends: US Adults - BMI
Prevalence of Self-Reported Obesity
U.S. Adults, 2013

Behavioral Risk Factor Surveillance System
Prevalence of Self-Reported Obesity
Non-Hispanic White Adults, BRFSS, 2011-2013

Behavioral Risk Factor Surveillance System
Prevalence of Self-Reported Obesity Hispanic Adults, BRFSS, 2011-2013

Behavioral Risk Factor Surveillance System

Data not reported*  15%–<20%  20%–<25%  25%–<30%  30%–<35%  ≥35%
Prevalence of Self-Reported Obesity
Non-Hispanic Black Adults, BRFSS, 2011-2013

Behavioral Risk Factor Surveillance System

Data not reported*
15%–<20%
20%–<25%
25%–<30%
30%–<35%
≥35%
Obesity Prevalence in Adult Men & Women By Race and Household Income

1. For all men, income was not a factor

2. For non-Hispanic black and Mexican American men, higher income had more obesity.

3. For all women, higher income had less obesity (non-Hispanic white)

Source: CDC/CNHS, National Health & Nutrition Survey, 2005-08

PIR: Poverty index ratio: Blue = higher income, Gray = lower income
1. Most obese people are not low income. -true for all races

2. The prevalence of obesity has risen for all regardless of sex, race, income, education.

Source: CDC/CNHS, National Health & Nutrition Survey, 2005-08

PIR: Poverty index ratio: Blue = higher income, Gray = lower income
1. For men: reduced prevalence for obesity with college education (non-Hispanic whites)

2. For women: reduced prevalence for obesity with college education (for all races)

Source: CDC/CNHS, National Health & Nutrition Survey, 2005-08

PIR: Poverty index ratio: Blue = higher income, Gray = lower income
Why do adults eat?

1. **Biology - Hunger**
   a. Empty stomach
   b. Hormones signaling metabolic status
   c. Sensing food - smells / sights
   d. Sleep deprivation - altered circadian rhythms

2. **Social cues**
   a. Habits - time of day, amounts, types of food
   b. Availability - ease of access / awake
   c. Social interactions / events

3. **Comfort - Stress - Addiction**
   a. Cravings, enjoyable
   b. Substitute for missing something else
   c. Stress relief
   d. Activates reward centers in brain
Why do adults stop eating?

1. Biology
   a. Full stomach (sometimes)
   b. Hormones signaling metabolic status
   c. Illness / aversion

2. Education
   a. Caloric content of foods - types of calories
   b. Recommended daily intakes - portions, timing
   c. Health risks

3. Emotional / Behavioral
   a. Social pressure for appearance
   b. Desire for health / Health scare
   c. Stress relief / support / treatment
   d. Substitute another stress reliever

4. Access - incidental or purposeful
   a. change social habits
   b. food is less available
Hormones affecting food intake and use

- Efferent Outputs
  - Appetite
  - Energy Expenditure
  - Hormonal milieu
  - Energy partitioning
  - Reproduction, growth

- Cerebral Nervous System (CNS)

- Leptin
  - Fat
  - Insulin
  - Pancreas
  - Long Term Afferent Signals

- Ghrelin
  - Stomach/small intestine
  - Meal Related Afferent Signals
  - PYY
  - GLP-1
  - CCK
Absence of Leptin or Leptin Receptors

Mice: No leptin on left

3 year old boy: no leptin production

Obese Zucker rat: No leptin receptors - lots of leptin, but no actions of leptin

Zucker rats

Same boy at 7 years with leptin treatment
Deficits in autonomic control of cardiovascular function with obesity: Insights from obese Zucker rats

Hey, I’m just big boned!
Obesity in humans: Deficits in cardiovascular control

**LONG TERM CONTROL**

Increased arterial pressure: obesity-induced hypertension

**SHORT TERM CONTROL**

Increased variability in mean arterial pressure

Decreased variability in heart rate: diagnostic marker (increases variability of arterial pressure)

↑ risk of cardiovascular disease & end organ damage
Arterial pressure = cardiac output \times \text{total peripheral resistance}

Cardiac output = \text{heart rate} \times \text{stroke volume}

TPR related to vasoconstriction and blood volume
Central and peripheral nervous systems

Central Nervous System
- Brain and spinal cord

Peripheral Nervous System
- Visceral
  - Visceral organs
- Sensory
  - Sensory organs
- Autonomic
  - Sympathetic
  - Parasympathetic
- Somatic
  - Skeletal muscle

OUTPUT

INPUT
Maintenance and reflex control of arterial pressure: Contributions from the central nervous system

\[ \text{AP} = \text{cardiac output} \times \text{total peripheral resistance} \]

Cardiac output = heart rate \times stroke volume
- \uparrow \text{by sympathetic inputs to heart}
- \downarrow \text{by parasympathetic inputs to the heart}

Resistance = constriction of vessels \times blood volume
- \uparrow \text{vessels: constriction by sympathetic nerves to blood vessels}
- \uparrow \text{kidneys: sympathetic nerves regulates blood volume}
Obesity in humans: Deficits in cardiovascular control

1. Increased arterial pressure: obesity-induced hypertension
2. Increased variability in mean arterial pressure
3. Decreased variability in heart rate: diagnostic marker

Increased risk of stroke and end organ damage

Associated autonomic dysfunctions
1. Elevated sympathetic nerve activity to heart, vessels, kidney
2. Impaired arterial baroreflex control of the circulation
Obese Zucker rats: A model for human obesity

1. Mutation of the receptor for leptin (Ob receptor) in OZR
   - high circulating levels of leptin, but leptin actions are absent

2. Increased food intake in OZR versus lean Zucker rats
   - increased meal size (leptin normally limits meal size)

3. Exaggerated weight gain in OZR compared to LZR
   - due to hyperphagia in OZR: diet-induced obesity

4. OZR have deficits in cardiovascular regulation analogous to obese humans
Obese Zucker rats develop elevated mean arterial pressure (hypertension)
Variability arterial pressure of mean is increased in conscious adult obese Zucker rats.
Variability of heart rate is reduced in conscious adult obese Zucker rats.
Homeostasis by negative feedback

Fall in room temperature below set point:
- Thermostat
  - Connecting circuitry
    - Furnace
      + Heat output raises Room temperature To set point

Fall in blood pressure below set point:
- Pressure-sensing nerve cells
  - Connecting brain circuitry
    - Heart and blood vessels
      + Increase in blood pressure to set point
Pathway for the baroreceptor reflex

If we use a drug to raise arterial pressure (constrict blood vessels)

The baroreflex is activated to reduce heart rate and sympathetic nerve activity to blood vessels.

These changes restore arterial pressure back to normal levels.
Obese rats develop hypertension and impaired baroreflexes.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (wks)</th>
<th>Body Wght (g)</th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZR (17)</td>
<td>7</td>
<td>206 ± 5</td>
<td>114 ± 2</td>
<td>447 ± 7</td>
</tr>
<tr>
<td>OZR (17)</td>
<td>7</td>
<td>289 ± 9*</td>
<td>115 ± 3</td>
<td>436 ± 6</td>
</tr>
<tr>
<td>LZR (30)</td>
<td>14</td>
<td>375 ± 5</td>
<td>116 ± 3</td>
<td>426 ± 3</td>
</tr>
<tr>
<td>OZR (34)</td>
<td>14</td>
<td>567 ± 7*</td>
<td>127 ± 2*</td>
<td>417 ± 4</td>
</tr>
</tbody>
</table>

![Graph showing SNA (% basal) vs Mean AP (mmHg) for LZR and OZR groups at 7 and 14 weeks.]
Preventing hypertension partially restores baroreflex.

Prevention of increased arterial pressure in obese rats....

....improves baroreflexes in obese rats* but they are still impaired†.
## Metabolic factors in juvenile & adult Zucker Rats

<table>
<thead>
<tr>
<th></th>
<th>Juvenile rats</th>
<th>Adult rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-7 weeks</td>
<td>13-15 weeks</td>
</tr>
<tr>
<td>age</td>
<td>Lean</td>
<td>Obese</td>
</tr>
<tr>
<td></td>
<td>204±4</td>
<td>313±13*</td>
</tr>
<tr>
<td>weight (g)</td>
<td>313±13*</td>
<td></td>
</tr>
<tr>
<td>blood pressure (mmHg)</td>
<td>122±4</td>
<td>121±4</td>
</tr>
<tr>
<td>glucose (mg/dl)</td>
<td>119±4</td>
<td>111±7</td>
</tr>
<tr>
<td>fasting insulin (ng/ml)</td>
<td>1.7±0.2</td>
<td>4.2±0.4*</td>
</tr>
<tr>
<td>cholesterol (mg/dl)</td>
<td>92±8</td>
<td>106±10</td>
</tr>
<tr>
<td>triglycerides (mg/dl)</td>
<td>81±6</td>
<td>202±13*</td>
</tr>
</tbody>
</table>

* indicates statistical significance.
Conclusions

1. Prevalence of obesity is on the rise in all adult groups.
2. Causes for obesity are clearly complex and challenging to prevent or treat – differ by population.
3. Obesity leads to impaired control of arterial pressure in the long term (hypertension) & short term (baroreflexes).
4. Both cardiovascular deficits independently increase risk for stroke and organ damage.
5. Hypertension and impaired baroreflexes are related but also caused independently.
6. Metabolic attributes of obesity may contribute.
7. Better prevention, detection and treatment of the cardiovascular consequences of obesity are needed.