Welcome to COGS163
The science behind metabolic disorders

EXPLORE THE SCIENCE associated with Metabolic Disorders

For example:

- What is the science of obesity?
- Is obesity a disease?
- What is the health impact of obesity?
- What is the genetic component of obesity?
- How does diet and exercise impact obesity?
- Is obesity a neurodevelopmental disorder?
- What are effective treatments?
Hormones

How do they control behaviors?

When and how do they wire your brain?

How can they change your metabolism?

What is their role in neurodegenerative diseases?

Insulin
Leptin
Ghrelin
FGF21
Orexin
Oxytocin

Hormones and Behaviors
1. Understanding Obesity

A brief tour of the class
Obesity

evolutionary perspective
I THINK THAT...
Is it fair to hold the morbidly obese responsible for their condition?
OBESITY AND DISEASE RISK
Health Consequences of Obesity

- Type 2 Diabetes
- Hypertension
- Coronary Heart Disease
- Fatty Liver Disease
Metabolic Syndrome: the principal cause of mortality in the developed world.
How is obesity defined and measured
Obesity:

1. Excessive amount of body fat in relation to lean body mass

2. Distribution of fat matters
BMI: BODY MASS INDEX

\[ BMI = \frac{\text{Weight (Kg)}}{\text{Height (m)}^2} \]
Correlation between BMI and %BF for Men in NHANES 1994 Data

%BF indicates excess adiposity in this quadrant while BMI does not. (N=695)

In this quadrant, BMI indicates excess adiposity while %BF does not. (N=1410)

https://commons.wikimedia.org/
The BOD POD

- The BOD POD is an Air Displacement Plethysmograph (ADP)
- It uses whole body densitometry to determine body composition (fat vs. lean).
- Similar in principle to underwater weighing methods.

http://ybefit.byu.edu/
What causes the variation in body fat?
Variability...

Which do you think is the single most important factor causing obesity?

- Lack of willpower?
- Lifestyle/environment?
- Biology/genes?
1st Law of Thermodynamics:

Energy input - Energy used = Δm Energy Stored

Change calories in change your body
Applies to people too – consider...

Food $\leftarrow$ intake

- Energy $\rightarrow$ burned

FAT STORED

1,000,000 cal/yr
Weight changes less than 10 pounds per decade!

99.6% precision
90 seconds?

How long can you hold your breath?
You can be highly motivated, but the basic drive will always win.
Eating food is a basic drive

- Breathing
- Sleeping
- Drinking
- Sex
- Eating
Basic drive to eat when you are hungry leads to diet failures.
LIFESTYLE AND ENVIRONMENT

Obesity rates are going up over time – so it must be the environment and lifestyle, right?
Obesity Levels are Rising

- 1999: 61% BMI > 25, 27% 25 < BMI < 30, 3% BMI > 30
Obesity is not new...

Venus of Willendorf

From Wikipedia, the free encyclopedia

The Venus of Willendorf is an 11.1-centimetre-tall (4.4 in) Venus figurine estimated to have been made 30,000 BCE.[1] [2] It was found on August 7, 1908 by a workman named Johann Veran[3] or Josef Veram[4] during excavations conducted by archaeologists Josef Szombathy, Hugo Obermaier and Josef Bayer at a paleolithic site near Willendorf, a village in Lower Austria near the town of Krems.[5][6] It is carved from an oolitic limestone that is not local to the area, and tinted with red ochre. The figurine is now in the Naturhistorisches Museum in Vienna, Austria.[7]

https://en.wikipedia.org/
Why is our perception so skewed?
Obesity categories (BMI)

- **Height = 5'10''**
- **Overweight**
  - Weight = 167 lbs
  - BMI = 24
- **Obese**
  - Weight = 209 lbs
  - BMI = 30
  - Weight = 279 lbs
  - BMI = 40
BMI 15 20 25 30 35

Obesity threshold
BMI 24.1

Obesity threshold
Why is weight so variable within a population?
Genes!
Tish & Miley Cyrus
adoptive parents

biological parents
Twin Studies:

- Monozygote
  - Share genes
- Dizygote
  - Share environment
Percent of the variance in the trait that can be accounted for genetic factors

heart disease
Alcoholism
Hypertension
Diabetes, Type 2
Schizophrenia

49%
.57
.57
.60
.68
.90
How heritable is obesity?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>.90</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>.68</td>
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<td>Diabetes, Type 2</td>
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<td>.57</td>
</tr>
<tr>
<td>Heart disease</td>
<td>.49</td>
</tr>
</tbody>
</table>
• Normal birthweight
• Morbid obesity beginning infancy
• Marked overeating
• Very high insulin levels
• Pre-diabetic at 4 yrs old
• 90 lbs with 50% body fat @ 4 years of age (normal is 20%)
• Highly inbred pedigree

20 YEARS OF LEPTIN

Human disorders of leptin action

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Abstract

The discovery of leptin has provided a robust framework upon which our current understanding of the mechanisms involved in energy homeostasis has been built. In this review, we describe how the identification of humans with mutations in the genes encoding leptin and the leptin receptor and the characterisation of the associated clinical phenotypes have provided insights into the role of leptin-responsive pathways in the regulation of eating behaviour, intermediary metabolism and the onset of puberty. Importantly, administration of recombinant human leptin in leptin deficiency represents the first mechanistically based targeted therapy for obesity and has provided immense clinical benefits for the patients concerned. In subsequent years, we and others have shown that human obesity can result from a multiplicity of defects in the pathways downstream of leptin signalling within the brain.

Key Words

- leptin
- receptors
- obesity
- signal transduction
I THINK THAT...
What is LEPTIN ??
Leptin

HYPOTHALAMUS

FAT TISSUE
Leptin

HYPOTHALAMUS

Leptin

FAT TISSUE
Leptin → HYPOTHALAMUS → FAT TISSUE → Leptin
Leptin

Hypothalamus

Food intake

Energy expended

Fat tissue

Less sensitive to leptin

Leptin

In obese
Inyect leptin?