Evidence Based Obesity Treatment

Richard D. deShazo, MD
Leigh Baldwin Skipworth, BA
University of Mississippi Medical Center
Jackson, Mississippi

Major Factors Affecting Mississippi’s Health

Access to Care

Health Literacy

Geography

Poverty

Race & Culture

Systems of Care

Prevalence of obesity among adults aged 2 and over; US 1997-June 2013

Hope?
Epidemiology 2

Prevalence of obesity among adults aged 20 and over by age group and sex US January – June 2013

--

MS Kids Count 2014 Data

Disparities in Mississippi School Children overweight or obese

--

America’s Health Rankings

--
Control of Eating Behaviors
Present Concepts
Satiety Cross Talk

Central and Peripheral Control of Eating Behavior

Central
- Arcuate nucleus of the hypothalamus controls food intake and energy balance to maintain homeostasis
- Cortical and subcontrol limbic system inputs can override hypothalamic controls (Hedonic stimuli)

Peripheral
- Gut, pancreas and fat neurochemical inputs are important in homeostasis

Hedonic influences
In response to sight, smell, taste, emotional and social factors, impulses from the cortex and limbic system under it are sent to the hypothalamus. These increase the desire for energy dense palatable food and override homeostatic regulation.
Peptides and hormones involved in appetite regulation

<table>
<thead>
<tr>
<th>Location</th>
<th>Agonists (↑)</th>
<th>Antagonists (↓)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Hypothalamus</td>
<td>POMC, Nesfatin, TRH</td>
<td>NPY, AgRP, Orexins, Orexins</td>
</tr>
<tr>
<td>Peripheral Gastrointestinal tract</td>
<td>CCK, GLP-1, PYY, Peptidylleukotrienes, Enterogastrin, Bombyxin, Urogastrin</td>
<td>Ghrelin</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Amylin, Insulin, VIP</td>
<td></td>
</tr>
<tr>
<td>Adipocytes</td>
<td>Leptin</td>
<td></td>
</tr>
</tbody>
</table>

Eating

Environment, human behavior, genetics

Activation of hedonic neuronal circuits in the amygdala, insula, orbito-frontal cortex

Hyperactive reward circuits to food stimuli

Pleasure

Overeating

Fat accumulation

Metabolic changes

Gut and fat hormones

Disease

Hypothalamic feeding circuits (homeostasis)

After King BM. Am Psychologist 2013

Mechanisms of Eating & Overeating

Commentary

Modern science versus the origins of obesity
Why Do People Overeat?

- The non-homeostatic brain reward circuitry that was acquired during evolution to seek out and eat as many nutritionally high-dense foods as possible is able to overrule the physiological inhibitory mechanisms that were designed to limit meal size and weight gain.
- When offered a variety of highly preferred foods, many will eat until feeling ill.


Fat and Inflammation Disease

- McArdle Front Endo 2013; 4:7 2013

Hypertrophic Adipocytes and M1 Macrophages
What is WAT?

Have Humans Trumped the Hypothalamus with the Cerebral Cortex?

- The biology of obesity appears to be more complex than calories in = calories consumed, stored or excreted.
- The hormonal hypothesis of obesity suggests that the kind of food consumed plays a role via appetite and satiety mechanisms. For instance, the types of carbohydrate (refined grains, starches and fructose) seem important.
- Since insulin is the primary hormone controlling fat deposition, insulin resistance also seems important.

Taubes G. Scient Amer. 2013; 309:60.

Questions Raised by Seeing Overeating as a Hormonal Not a Behavioral Disorder?

- Palliative foods override normal weight control mechanisms.
- Obese individuals generally have a paradoxically high level of appetite suppressing hormones, including leptin and insulin.
- May obesity seen as a “disease”?
- Are obese individuals “victims”?

Kenney PJ. The Food Addiction. New brain research is revealing why fats and sugars may be driving more and more people toward obesity. Would a rat risk dying just to satisfy its desire for chocolate? Scientific American. 2013; 309:44.
Food Science and the FLAVOR Connection

*How Flavor Chemists Make Your Food So Addictively Good*

> Kupferschmidt K. Following the Flavor. Science 2013; 340:808-809

---

Increasing Scientific Support of Factors Favoring Overeating

- (Hyper)Palatable Processed Foods (salt/sugar/fat/calorie dense)
- Super-sizing
- Low cost/availability
- Sedentary life style
- Normative behavior
- Habituation/addiction

---

Food Science, Taste & Flavor

The oral sensations of food in the mouth are taste, retronasal-olfaction (smell) and chemosensation (heat).

- **Taste** is composed of five oral perceptions (sweet, salty, sour, bitter and umami (savory)). It is assessed with nose clips
- **Flavor** = Taste plus retronasal olfaction (Smell) and is assessed without nose clips
- **Flavor and heat** are chemically modified in processed foods

---
Food Science and Taste

Foods with certain mixtures of salt, sugar and fat are especially pleasurable (palatable) and stimulate pleasure (hedonic) centers in the brain.

- Energy dense foods (fat, sugar) are more palatable than low-energy dense foods and promote their ingestion over satiety.
- Salt inhibits bitterness from oxidation of fatty acids with cooking of fat and makes it palatable.
- Hyper-insulinemia, hyper-leptinemia and leptin resistance also influence taste.

fMRI in Obese Subjects Show

- Satiety centers (caudolateral orbitofrontal cortex) that promote sensory-specific satiety are less active in obese as compared to lean individuals.
- There are decreased brain dopamine receptors in obese subjects that could result from:
  - Overeating to compensate for fewer receptors and under activation of reward circuits or
  - Down-regulation of dopamine receptors from high dopamine levels from overeating.

fMRI are informative in Food Science and Obesity Research
Fructose (corn syrup) vs Sucrose (glucose) Studies

Potential of magnetic resonance imaging measures for enhanced product development

Paul Smeets1,2
1 Division of Human Nutrition, Wageningen UR
2 Image Sciences Institute, Utrecht University

Results

- Higher brain activation by food cues in reward areas (orbitofrontal cortex, striatum) in a low- vs a high-protein state
- When exposed to high-calorie food cues, brain activation was higher in the orbitofrontal cortex
- Only an effect of taste quality (savory), not of protein content (1)

References:
(References, if any)
Diets

Weight Loss Improves Risk Factors for CV Disease in Young People

- 5-10% weight loss via lifestyle changes reduces CV risk factors, delays onset of type 2 diabetes, and improves other health consequences of obesity. Greater weight loss has greater benefit.  
- Regain of weight can be attenuated but not eliminated by continued lifestyle treatment.  
- Additional approaches are needed.


Why Diets Don’t Work: They Make You Hungry

- Calorie restriction increases fMRI activity in hypothalamic and midbrain areas associated with attention, reward, motivation and taste

- On-diet changes in appetite regulating hormones promote weight gain with decrease in levels of leptin, PY4, CCK, insulin, amylin (all decrease appetite normally), increase ghrelin

- Sympathetic overdrive associated with obesity persists and may cause down-regulation of adrenergic receptors with impairment of fat metabolism, etc.

2. Cornier PLOS One 2009; 4:e6310,  
Is “Food Addiction” the Explanation of Obesity?

- DSM-5 has no “food addiction” category
- Most obese individuals do not demonstrate aberrant patterns of food consumption, or the psychopathology and behavioral disturbances associated with addiction.¹
- DSM-5 established binge-eating disorder (BED) as a free-standing entity
- Diagnosis of BED requires binge-eating average once a week for 3 months
- Animal and human research suggest that drug and food addiction have a common biology²,³


Is “Food Addiction” the Explanation of Obesity?
Consensus View

- The most likely psychological factors associated with being overweight or obese are:
- Decreased self-control required for restraint when exposed to the obesogenic foods and food-like palatable substances¹
- Increased sensitivity to reward stimuli of palatable food²
- “Self-medication” of mood disorders or pain using palatable foods³
- Co-existing psychiatric disturbances with compulsive features⁴


A Range of Diets with Various Fat, Protein, & Carbohydrate Compositions are Effective in Weight Loss & Have Similar Effects at 2 Years

- NEJM 2009; 360: 859
How Best to Lose Weight?

- Diets?
- Which One?
- 15 studies of behavior, diet and lifestyle modification in obese individuals showed a weight loss of 3.43 pounds at 1 year (NS)

Dombrowski BMJ 2014; 348:g2646doi.
Present Preferred Bariatric Surgical Operations for Severe Obesity

- Acute post-op complications (<10%)
- Chronic post-op complications: leak, infection, PE, stricture, obstruction, fistula, band slippage, nausea, bone loss, nutritional deficiency
- Outcomes: weight loss at 1 year - bypass 158.4 lb, sleeve 152.68 lbs, band 73.5 lbs ~50% of excess weight loss over IBW at 15 years
- Sleeve gastrectomy = gastric bypass in weight loss over banding with fewer complications


Gastropexy or Gastric Bypass

227 gastroscopy and 55 gastric bypass vs 260 medically managed controls followed for ~18 years in a retrospective evaluation at 25 surgery sites in Sweden. Men and women with BMI >34 or 38 and diabetes.
Drug Treatment of Obesity: The No Silver Bullet Principle

In contrast to drugs whose effects are exerted directly at the level of the brain reward dopamine pathway, food affects multiple peripheral and central mechanisms that directly and indirectly convey information to the brain’s DA reward pathway. The hypothalamus plays a particularly prominent role in this regard although it is also strongly implicated in drug reward.

Two Important Reports on Drug Treatment for Obesity

- Conclusions: “FDA medications approved for weight loss plus lifestyle modification lead to (a) greater weight loss and (b) greater maintenance of weight loss than placebo. There is little prospect for weight loss in those who do not lose at least 5% of body weight by 12 weeks of treatment.”

Yanoski. JAMA 2014; 3:74
FDA Approved Weight Loss Drugs (1)

- Centrally Acting Noradrenergic Agents: Approved for only 12 weeks
  - Phentermine, diethylproprion, phendimetrazine, benzphetamine (BMI >30)
  - Activate adrenergic and dopaminergic receptors
  - No long term trials for efficacy or side effects that meet present FDA trial requirements
  - Phentermine is the most popular (15-30 mg/day)
  - Many short term studies done before present FDA requirements for efficacy.
  - No long term trials meeting existing guidelines.

  a. Approved for use for BMI>30 or BMI>27 plus 1 or more comorbid condition. b. adipex c. tenuate d. bontril e. didrex

FDA Weight Loss Drugs (2) Approved for Long Term Use

- Decreased Lipid Absorption
  - Orlistat (Xenical), approved in 1999, (60mg OTC, 120mg RX) TID inhibits fat absorption by 30%
  - Effective
  - Because of GI side effects. Less than 10% take for 1 year and less than 2% take for 2 years

FDA Weight Loss Drugs Approved for Long Term Use(2)

- Serotonin Receptor Activator (Belviq)
  - Lorcaserin (Belviq) (10mg BID) approved in 2012, is a selective 5HT(2C) receptor antagonist substitute for fenfluramine
  - Bloom, Blossum and Bloom DM trials show around 3.4% weight loss at one year. "22% greater weight loss than controls on calorie control and exercise.
  - FDA required long term trials for assessment of CV efforts.

FDA Weight Loss Drugs Approved for Long Term Use(3)

- Combination Therapy (Qsymia)
  - Phentermine plus topiramate ER 3.75/23
  - Qsymia (startup 7.5/46, 11.2/69, 15/92 QD doses) approved 2012 with post-marketing requirement for CV toxicity.
  - For patients with BMI over 30 or 27 with risk factors
  - Trials show benefit in weight 8.6% - 9.4% loss and risk factor improvement with 50% more weight loss than controls
  - Every month pregnancy test for topiramate teratogenicity required.


Present NIDDK Recommendations on Weight Loss Drugs1

- Drugs that will probably result in a 5% or greater weight loss at 1 year:
  - Orlistat
  - Lorcaserin
  - Phentermine+Topiramate SR
  - Long term side effects not assessed2
  - Pipeline
    - Contrave (bupropion and naltrexone) (FDA did NOT approve, but granted a 3 month extension for more time to review)
    - Liraglutide (5% wt loss at 1 yr) not approved


Frequent Side Effects Reported with Recommended Drugs in Clinical Trials

- Phentermine/Topiramate – HA, constipation, insomnia, paresthesia, dysgeusia, dry mouth
- Lorcaserin – dry mouth, fatigue, dizziness, HA

Conclusions
What’s Good and What’s Bad?

<table>
<thead>
<tr>
<th>Bad</th>
<th>Good</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity plus</td>
<td>Normal weight</td>
<td>AVOID processed foods!</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diets and exercise</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>for a few</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Drugs for a few</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Bariatric surgery,</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>exercise and diets</td>
<td></td>
</tr>
<tr>
<td>7 years life</td>
<td>for many</td>
<td></td>
</tr>
</tbody>
</table>

2014 Bibliography 1
- Moss MW. The extraordinary science of addictive junk food. NYT, Feb 20, 2013.
- Davis D. From passive overeating to “food addiction”: a spectrum of compulsion and severity. JAMA 2012; Article ID 435 027.

2014 Bibliography 2
Bibliography 3