Overeating of sugars and fats: Links to addiction and obesity following *in utero* or adult exposure

(note that slides with unpublished data have been removed)

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Outline of the talk

- What does nutrition have to do with drug addiction?
- Background on feeding behavior and its associated brain systems
- Drugs and sugar: similarities and differences
- Assessing “food addiction”: a gateway to subsequent drug use?
- Can other palatable tastes produce signs of addiction?
- Effects of body weight and food choice (variety)
- Epigenetic effects of overeating
Addiction: It isn’t just for drugs anymore...

- Natural behaviors, such as mating, can be addictive
- Gambling, Internet, Video games
The BIG Problem: Drug Addiction

Drugs abuse leads to *other* drug abuse

- Drugs of abuse can be gateways to using more or other drugs
- Can other addictions be gateways to drug use, or vice versa?
The OTHER BIG Problem: Obesity in the US

- 64.5% of adults in the U.S. are overweight, and 30.5% are obese (CDC 2010, shows 35.7% of adults are obese).
- Being obese or overweight can lead to comorbid health concerns (e.g., heart disease, diabetes).
- Increased body weight can have psychological, economical, and social consequences.
Why are so many people overweight?

- Foods that are rich in fats and sugar, and consequently calories, taste good.
- Palatable food is ubiquitous for most people in our society.
- Food is a part of our social lives.
- People eat for reasons other than hunger (e.g., boredom, stress, etc.).
What about the idea of “food addiction”?  

- Could some people be “addicted” to eating sweets and fats, in ways that resemble drug addiction?  
- Out-of-control eating could result in increased body weight and obesity.
How do drugs of abuse and food exert their reinforcing/pleasurable effects?

- There are overlaps in the brain pathways activated by palatable foods and drugs of abuse.
- Drugs act on brain systems that evolved to reinforce natural behaviors (e.g., sex, feeding).
- Thus, the circuitry is in place for food to be addictive.
What is an addiction?

- Bingeing
- Craving
- Cross-sensitization
- Enhanced locomotion
- Increased consumption
- Withdrawal
- Tolerance
- Negative emotion
- Anticipation
Drugs of abuse vs. food

- **DA** - Reinforcement/orienting. Abused drugs increase extracellular DA each time they are administered.
- **ACh** - Aversion. ACh is increased during withdrawal (DA is low).
- **Opioids** - antagonists precipitate withdrawal signs.

- **DA** - Motivation to eat. With food, DA release wanes with repeated access.
- **ACh** - Satiety. ACh increases during a meal (DA is high).
- **Opioids** - antagonists do not precipitate withdrawal signs.
Animal model of sugar addiction
THE GLOBAL SUGAR GLUT

Global sugar supply (in the form of sugar and sugar crops, excluding fruit and wine) expressed as calories per person per day, for the year 2007.
Sugar-sweetened Beverages

- Intake is associated with obesity, globally (Popkin et al., 2011)
- Soft drinks and fruit juices dominate
Design

- Sprague-Dawley rats are maintained for ~1 mo on 12-h daily (binge) access to a 10% sucrose solution and standard rodent chow, followed by 12-h deprivation. Water is available *ad libitum*.

Why bingeing?

- Bingeing is seen in people who are obese, and also in the general population.
Day 1 of Glucose Access

Day 21 of Glucose Access

From Avena et al., 2008
Tolerance

Both from Rada, Avena, and Hoebel (2005)
In vivo microdialysis to measure extracellular DA and ACh in the NAc

Methods:
• Sprague-Dawley rats with guide cannulas aimed at the NAc shell
• Maintained on one of 4 diets:
  1. Daily Intermittent Sucrose + Chow
  2. Daily Intermittent Chow
  3. Daily Ad libitum Sucrose + Chow
  4. Sucrose Twice
• Microdialysis performed on Days 1, 2 and 21
DA release in sugar-bingeing rats

Dopamine repeatedly increases in sugar bingeing rats, but not in control rats.

* From Rada, Avena and Hoebel (2005)
Does the taste of sucrose repeatedly release accumbens DA?
The taste of sucrose while bingeing is sufficient to repeatedly release accumbens DA

From Avena, et al.(2006)
Withdrawal

Signs of opiate-like withdrawal seen following removal/withdrawal from sugar:

- Anxiety
- Wet-dog shakes
- Tremor
- Depression
- Aggression

Sugar bingeing rats show signs of anxiety when given an opioid antagonist (naloxone) or fasted.

From Avena et al., 2008
Withdrawal is concurrent with decreases extracellular DA and increases ACh levels in the NAc

\[\text{Dopamine (Percent of Baseline)}\]

\[\text{Acetylcholine (Percent of Baseline)}\]

*From Avena et al., 2008*
Sugar-bingeing rats are hyperactive in response to a low dose of amphetamine 8 days after they stopped drinking sugar.

From Avena and Hoebel, 2003
Sugar-bingeing rats drink more 9% ethanol compared with controls

From Avena et al., 2004
Summary of findings of sugar addiction using this model

Table 1
Summary of findings in support of sugar addiction in rats using an animal model of sucrose or glucose bingeing.

<table>
<thead>
<tr>
<th>Substance dependence</th>
<th>Animal model of sugar dependence</th>
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<tbody>
<tr>
<td><strong>A. DSM-IV-TR</strong></td>
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<tr>
<td>Tolerance</td>
<td>Escalation of daily sugar intake (Colantuoni et al., 2001)</td>
</tr>
<tr>
<td>Signs of withdrawal</td>
<td>Somatic signs (teeth-chattering, tremor), Anxiety measured by plus-maze,</td>
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<tr>
<td></td>
<td>Ultrasonic distress vocalizations (Colantuoni et al., 2002 and Avena et al., 2008)</td>
</tr>
<tr>
<td>Consuming more than intended</td>
<td>Deprivation effect (Avena et al., 2005)</td>
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<td><strong>B. Behavioral signs</strong></td>
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<tr>
<td>Locomotor cross-sensitization</td>
<td>Amphetamine (Avena and Hoebel, 2003)</td>
</tr>
<tr>
<td>Proclivity to consume other drugs of abuse</td>
<td>Alcohol (Avena et al., 2004)</td>
</tr>
<tr>
<td><strong>C. Neurochemical changes in the NAc</strong></td>
<td></td>
</tr>
<tr>
<td>Repeated release of DA</td>
<td>Rada et al. (2005) and Avena et al. (2006)</td>
</tr>
<tr>
<td>↑ D₁ receptor binding</td>
<td>Colantuoni et al. (2001)</td>
</tr>
<tr>
<td>↓ D₂ receptor binding</td>
<td>Colantuoni et al. (2001)</td>
</tr>
<tr>
<td>↑ D₄ receptor mRNA</td>
<td>Spangler et al. (2004)</td>
</tr>
<tr>
<td>↓ preproenkephalin mRNA</td>
<td>Spangler et al. (2004)</td>
</tr>
<tr>
<td>DA/ACh imbalance during withdrawal</td>
<td>Colantuoni et al. (2002) and Avena et al. (2008)</td>
</tr>
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</table>

Moving beyond sugar to other palatable foods: Can they be addictive?
The problem revisited: Obesity?

- Our sugar bingeing model does not result in increased body weight.
- Rats regulate their caloric intake by eating less chow.
- Similar findings seen with fat (Corwin’s group).

From Avena et al., 2008
Combinations of nutrients (sugar/fat) seems to increase body weight

- Sweet-Fat bingeing rats are hyperphagic.

- Overall, sweet-fat bingeing rats have an increased body weight.

From Berner et al., 2008
But fat bingeing does not result in opiate-like withdrawal...

We experimented with different types of fats (complete diet, vegetable fat, oil), schedules of feeding (short, long access), forms (solid, liquid), and were unable to elicit the signs of opiate-like withdrawal that emerge with naloxone or spontaneously in sugar-bingeing rats.

From Bocarsly et al., 2011
Fat may release or affect neurochemicals that counteract the opiate-like withdrawal

Galanin?
- Galanin protects against behavioral and neurochemical correlates of opioid reward (Hawes et al., 2008)

Endocannabinoids?
- link between dietary fat and endocannabinoids
- increased endocannabinoids attenuates opiate withdrawal (Ramesh, 2011)
Sugars vs. fats: What does it means for “food addiction”? 

- Fats and sugars may produce different types of behaviors associated with addiction.
- The definition of “food addiction” can be refined and perhaps treated pharmacologically by looking more carefully at the behavioral effects of certain nutrients.
- This may be complicated by the variety of palatable ingredients used in creating palatable food choices.
Obesity and food choice
Variety and hyperpalatability: are they promoting addictive overeating?¹⁻³

Nicole M Avena and Mark S Gold

- Variety in foods attenuates habituation to food in humans (Epstein et al., 2009).....when you have variety, you eat MORE.
- Cafeteria-style diet produces signs of opiate-like withdrawal in rats (Le Magnan et al., 1990).

What happens when we have a variety of food choices, all of which are hyperpalatable?
Cafeteria-diet induced obese rats are hyper-responsive to amphetamine, but don’t respond to a lab chow meal. These rats need a “junk food” diet to release accumbens DA.

*From Geiger et al., 2009*
Food-to-Drug Abuse Seen in Humans
Drug abusers have low brain DA activity (shown here using $[^{11}\text{C}]$raclopride PET studies) indicating an understimulated reward system.

Decreased Dopamine D2 Receptors in Obese Human, Monkey and Rodent

**Human**

- **BMI = 23**
- **PET [11C]raclopride**

**Bonnet macaques**

- **BMI = 23**

**Zucker rat**

- **Weight = 400 g**
- **Weight = 650 g**
- **ARG [3H]spiperone**

ARG, autoradiography; PET, positron emission tomography

Food addiction in obesity

Evidence that ‘food addiction’ is a valid phenotype of obesity

Caroline Davis a, b, *, Claire Curtis a, Robert D. Levitan b, Jacqueline C. Carter c, Allan S. Kaplan b, James L. Kennedy b

Appetite 57 (2011) 711–717

<table>
<thead>
<tr>
<th>Variable</th>
<th>Food addict Mean (SD)</th>
<th>Non-food addict Mean (SD)</th>
<th>p</th>
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<tbody>
<tr>
<td>Impulsivity</td>
<td>73.2 (12.0)</td>
<td>62.2 (10.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Addictive traits</td>
<td>16.2 (6.2)</td>
<td>12.5 (3.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Delay of gratification</td>
<td>35.9 (22.1)</td>
<td>47.8 (19.7)</td>
<td>0.036</td>
</tr>
<tr>
<td>Delay discounting (total)</td>
<td>231.7 (138.2)</td>
<td>306.5 (123.2)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Neural Correlates of Food Addiction

Ashley N. Gearhardt, MS, MPhil; Sonja Yokum, PhD; Patrick T. Orr, MS, MPhil; Eric Stice, PhD; William R. Corbin, PhD; Kelly D. Brownell, PhD
Epigenetics effects of diets
• In utero exposure to drugs of abuse affects development and can promote addiction in offspring.
• Maternal obesity during pregnancy increases the risk of obesity in offspring.
• Diet in utero can have long-lasting effects on food intake and preference (Dutch Winter Famine).
• High-fat diet in utero can affect DA- and opioid-ergic gene expression in offspring (Reyes et al., 2010).
Conclusion

- Fats and sugars may produce different types of behaviors associated with addiction.
- Food addiction can lead to increased drug sensitivity and intake, even when animals are not obese.
- Overeating during the prenatal period can reprogram the brain in a way that promotes drug intake later in life.
Thank you!

Collaborators:
Mark Gold
Bart Hoebel
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Melissa Moyer
Brandon Chan
Miaoyuan (May) Wang
Cindy Kroll
Susan Murray

Funding:
NIH (K01-DA031230-01)

National Eating Disorders Association

University of Florida

Kildehoj-Santini