Psychopharmacology of Eating Behavior
Obesity: A Global Epidemic

34% of all Americans are overweight; 30.5% are obese.

15% of adolescents in the US are now seriously overweight.

Raises risk for heart disease, diabetes, stroke, high blood pressure, cancer and other chronic diseases; 300,000 premature deaths per year.

[CDC, 2006]
Eating-Related Disorders

Anorexia Nervosa

Severe calorie restriction; purging.

Mostly affects females (90%); but increasing in males
Anorexia Nervosa

Etiology –

Psychological; Obsession with thinness;
Personality traits
Struggle for personal autonomy
Life changes; Stressful events
Sexuality

Biological Predisposition
Genes, hormones, neurotransmitters
Binge Eating Disorder; Bulimia Nervosa

Depression, stress, anxiety, dieting, coping skills.

Biology: Brain neurotransmitters; metabolism (the way the body uses calories); impulsivity; genes.
Evidence for Brain Involvement?
Adapted from Teitelbaum, 1961
# Neurotransmitter Effects on Eating Behavior

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>CNS Receptor</th>
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<tr>
<td><strong>Eating Stimulatory</strong></td>
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<tr>
<td>Norepinephrine</td>
<td>Paraventricular nucleus</td>
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<tr>
<td>Neuropeptide Y (NPY)</td>
<td>Hypothalamus</td>
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<tr>
<td>Galanin</td>
<td>Hypothalamus</td>
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<tr>
<td>Opioid peptides</td>
<td>Hypothalamus</td>
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<tr>
<td>Glutamate</td>
<td>Lateral hypothalamus</td>
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<td>GABA</td>
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<tr>
<td>Serotonin (5-Hydroxytryptamine, 5-HT)</td>
<td>Medial hypothalamus</td>
</tr>
<tr>
<td>Dopamine, Epinephrine</td>
<td>Lateral hypothalamus</td>
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<tr>
<td>Cholecystokinin</td>
<td>Hypothalamus-hindbrain</td>
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<tr>
<td>Bombesin, Neurotensin</td>
<td>Hypothalamus-hindbrain</td>
</tr>
<tr>
<td>Leptin</td>
<td>Hypothalamus</td>
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<tr>
<td>Glucagon</td>
<td>Lateral Hypothalamus</td>
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<tr>
<td>Glucagon-like peptide-1 (GLP-1)</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Corticotropin releasing factor</td>
<td>Paraventricular nucleus</td>
</tr>
<tr>
<td>Urocortin, Melanocortins</td>
<td>Hypothalamus</td>
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<tr>
<td>Other gut-brain peptides</td>
<td>?</td>
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</tbody>
</table>
Neuropeptide Control of Ingestive Behavior

1. Neuropeptide Y: An Orexigenic Neurotransmitter
2. NPY Interacts with Serotonin and Leptin
3. Ghrelin: A Novel Gut-Brain Peptide
4. How is Ghrelin different from NPY?
Neuropeptide Y (NPY)

- 36 amino acid peptide widely distributed in the mammalian brain.
- Produced by neurons of the arcuate nucleus; project to paraventricular nucleus.
Arcuate Nucleus NPY Cell Bodies
Paraventricular Nucleus NPY

- Chronic injection can lead to a two-fold increase in daily food intake.
- Triple body fat after a 10-day injection period.
NPY Receptor

Y1: Analgesia, Eating, Hypertension
Y2: Analgesia, Anorexia, Memory
Y4: Eating

Y5: Pseudogene in humans.

[Chamorro et al., 2002]

Molecular structure of some currently known non-peptide Y receptor antagonists.
NPY Receptor Pharmacology

Stimulation of Eating

Y1 and Y5 receptor agonists increase eating

Antagonists block eating
Where does NPY act within the brain to stimulate eating?
Hypothalamic NPY-Induced Eating

![Graph showing food intake (g) vs. NPY (pmol) for different regions: PVN, VMH, PFH.](image)
But it’s not just eating.............
Energy Metabolism

How we use calories/energy

RQ

Energy Expenditure
NPY’s Interaction with Other Hypothalamic Neurotransmitters
Serotonin (5-HT) Receptors

- $5\text{-HT}_{1A, B, D, E}$
- $5\text{-HT}_{2A, B, C}$
- $5\text{-HT}_{3}$
- $5\text{-HT}_{4}$
- $5\text{-HT}_{5A, B}$
- $5\text{-HT}^{6}$
- $5\text{-HT}_{7}$

[Cooper et al., 2003]
Indirect and Direct 5-HT Agonists

Reduce intake in free-feeding and food-restricted rodents.

Acts via an increase in synaptic 5-HT or direct binding to postsynaptic receptors.
## Effects of 5-HT Agonists on NPY Eating and RQ

<table>
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<tr>
<th>5-HT Receptor</th>
<th>Agonist</th>
<th>Food Intake</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>8-OH-DPAT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1B/1A</td>
<td>RU 24969</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1D</td>
<td>L-694,247</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2A/2C</td>
<td>DOI</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2B</td>
<td>BW 723C86</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2C</td>
<td>mCPP</td>
<td>-</td>
<td>-</td>
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</table>
Is 5-HT the only neurotransmitter acting to antagonize the feeding and metabolic action of hypothalamic NPY?
The Anorectic Effect of Leptin

![Bar chart showing the effect of PVN Leptin (pmol) on food intake (g)].

- **Veh**: 0
- **12.5**: 2
- **25.0**: 4
- **50.0**: 0
Leptin Suppresses NPY-Induced Eating

Leptin + NPY (100 pmol)

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<th>Veh</th>
<th>12.5</th>
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* indicates statistical significance.
1. Fat cells secrete leptin into circulation.

2. Leptin reaches leptin receptors in hypothalamic regions.

3. Leptin receptor activation suppresses neuropeptide production and release.

4. Leptin inhibits arcuate neurons releasing NPY and AGRP, but excites neurons releasing αMSH. NPY-receptive neurons releasing αMSH.

5. Leptin receptor activation also increases levels of corticotropin-releasing hormone, which suppresses hunger.

[Adapted from Rosenzweig et al., 2005]
Eating Disorders: Biological Focus

Humans: Brain Neurochemistry

Altered peptide (NPY; PYY; CCK; Leptin) and monoamine (NE, DA and 5-HT) levels in CSF in eating disorder patients.

Similar observations in genetic obesity – animal models.
Clinical Use of Serotonergics

5-HT agonists

Help to reduce excessive food intake

May also reduce depression and anxiety
Anorexia Nervosa: Treatment

Appetite Stimulants
  Limited success

Cognitive Behavior Therapy and Drug Treatment
  Drug: Stabilize
  Behavior modification, nutrition counseling
Ghrelin: A Novel Hypothalamic Peptide
Hungry? It Could Be Biochemical

Appetite is largely controlled by a complex system of molecules that evolved over millions of years. They travel between the body and the brain, and within the brain itself.

**NEUROPEPTIDE Y**
A protein that acts as a transmitter in the nervous system and helps stimulate food intake as well as regulate metabolic rate and fat formation.

**GHRELIN**
A hormone made in the stomach and intestine. It is a powerful appetite stimulant.

**PYY**
Peptide YY3-36, or PYY, is made by cells in the intestine in response to food. It then circulates to the brain, where it switches off the urge to eat.

**LEPTIN**
Made by fat cells. When levels are normal, people eat just enough to maintain their weight. But leptin's absence signals the brain that the body lacks fat reserves. This can result in overeating.

How PYY Helps Control Eating

1. The arcuate nucleus in the hypothalamus receives signals from the body and determines whether food is needed. Its two types of neurons are triggered by PYY.

   - Neurons that make you feel full.
   - Neurons that make you hungry.

   Pyy turns them on.

2. The neurons send the appropriate signal (eat or don't eat) to the paraventricular nucleus. There, neurotransmitters for hunger or fullness are released.

3. The paraventricular nucleus sends signals giving priority either to feeding or to activities that use energy, including movement and growth.

4. Appetite is either triggered or suppressed.
Ghrelin Levels in Dietary Obesity
Orexigenic Effect of Ghrelin

**Arc N. Ghrelin (pmol)**

![Food Intake Graph for Arc N. Ghrelin](image)

**PFH Ghrelin (pmol)**

![Food Intake Graph for PFH Ghrelin](image)

**PVN Ghrelin (pmol)**

![Food Intake Graph for PVN Ghrelin](image)

**VMN Ghrelin (pmol)**

![Food Intake Graph for VMN Ghrelin](image)
Effect of Ghrelin on Energy Metabolism (RQ)

![Graph showing the effect of ghrelin on energy metabolism (RQ) over time. The graph includes data points for VEH male, VEH female, ghrelin (30 pmol) male, and ghrelin (30 pmol) female.](image)
But How is Ghrelin Different?
Elevated Plus Maze and Anxiogenic Behaviors
Anxiogenic Effect of Ghrelin after Injection into the Hypothalamus (Arcuate Nucleus)
Ghrelin and Stereotypic Behavior

Prolonged rearing
Oral stereotypies
Excessive grooming
Wet dog shakes
Sensitivity to Noise
How is Ghrelin Unique?

Ghrelin is the only orexigenic peptide reported to increases anxiety.
Where do we go from here?

Ghrelin’s Interaction with Endocannabinoids

Cannabinoids: chemicals structurally related to tetrahydrocannabinol (THC)
Ghrelin and Cannabinoids

- Drugs that block cannabinoid receptors in the hypothalamus potentiate ghrelin-induced eating and anxiety.
Conclusions

• Eating behavior is influenced by many factors including biological, psychological, social and environmental variables.

• Homeostatic mechanisms (Hypothalamus)

• Stress/anxiety (Limbic)

• Reward circuits
Mesotelencephalic Dopamine System

- Prefrontal cortex
- Striatum
- Septum
- Hippocampus
- Ventral tegmental area
- Olfactory tubercle
- Nucleus accumbens
- Amygdala (in temporal lobe)
- Substantia nigra