Neurohormonal Mechanisms of Obesity – The Role of the Brain

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Disclosures

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Homeostatic Regulation of Set Point Body Weight
A homeostatic weight regulatory system prevents deviation from a body weight set point

Deviation from this set point elicits a physiological compensatory mechanism controlling food intake and energy expenditure

Two Centers of the Brain Are Involved in Food Intake and Energy Balance

Hypothalamic Reward System
- Region of the brain that controls the motivation, reward, and reinforcement associated with survival activities (e.g., eating, reproduction)
- Dopaminergic and opioid signaling known to play important roles
- Activity is seen to be altered in obese population

Mesolimbic Reward System
- Can override the hypothalamic hunger system
- Increasing the consumption of highly palatable foods

Peptides Modulate Appetite and Energy Expenditure in the Arcuate Nucleus of the Hypothalamus
The hypothalamic hunger system

The hypothalamus contains 2 major opposing pathways that affect appetite and energy expenditure.

<table>
<thead>
<tr>
<th>POMC neuron activation</th>
<th>Increases appetite</th>
<th>Reduces energy expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgRP/NPY neuron activation</td>
<td>Decreases appetite</td>
<td>Increases energy expenditure</td>
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The hypothalamus contains 2 major opposing pathways that affect appetite and energy expenditure.

- AgRP/NPY neuron activation
  - Decreases appetite
  - Increases energy expenditure

- POMC neuron activation
  - Increases appetite
  - Reduces energy expenditure

Hypothalamus

POMC neurons’ role in hunger

- POMC neurons
  - Decrease multiple energy balance signals
  - Bind to MC4-R to decrease food intake

POMC neuron activation

- Decreases appetite
- Increases energy expenditure

- Increases appetite
- Reduces energy expenditure

β-endorphin (endogenous opioid)

- Released from POMC neuron
- Binds to µ-opioid receptor to inhibit POMC neuron activation (negative feedback loop)

Circuits through which leptin normally acts

- We know the pathways through which leptin normally acts
- Have a detailed understanding of how body weight is regulated
  - At a molecular level
  - At a neuron level
  - And on a brain circuit level
- Our circuit model explains how serotonin modulators regulate body weight
- Circuit model explains how melanocortin agonists cause weight loss
- We know that leptin can no longer activate or inhibit neurons in a leptin resistant brain

Can we design a therapy that works on the same neuronal pathways as leptin does?

Naltrexone and bupropion act synergistically to activate the POMC neurons in the hypothalamic hunger system, resulting in appetite suppression.

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<table>
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<th>POMC Neuron Activity</th>
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<tr>
<td>10 µM BUP + 1 µM NAL</td>
</tr>
<tr>
<td>1 µM NAL</td>
</tr>
<tr>
<td>10 µM BUP</td>
</tr>
</tbody>
</table>

Figure adapted from Billes et al. 2014. Pharmacological research 84, 1-11.
**Mesolimbic Reward System**

- Center of the brain that mediates the motivation, reward, desire, pleasure, and reinforcement associated with activities needed for survival (e.g., eating, reproduction)\(^1\)
- Centers of dopamine and opioid receptor signaling\(^1\)
- The Mesolimbic Reward System evolved to respond to high-fat, high-sugar foods to aid survival\(^1,4\)
- Associated with reward-based eating behavior and cravings in a pleasurable environment\(^1,4\)

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**Evidence Supports Altered Mesolimbic Reward System Activation in Patients With Obesity**

**Fasted/Hungry State**
- Individuals with obesity have greater reward system activation in response to pictures of high-calorie foods compared with lean individuals\(^7\)

**Fed/Satiated State**
- Individuals with obesity still show reward system activation following a meal when exposed to food cues vs lean individuals who have reduced reward system activation\(^11\)

*Images represent statistical differences in fMRI activation in response to food cues between obese and lean individuals (absent/bottom).*

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**Combination Naltrexone + Bupropion Resulted in Greater Weight Loss vs the Individual Components\(^1\)**

<table>
<thead>
<tr>
<th>Component</th>
<th>Weight Loss</th>
</tr>
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<tbody>
<tr>
<td>Naltrexone</td>
<td>-3.1%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>-3.1%</td>
</tr>
<tr>
<td>Naltrexone + Bupropion</td>
<td>-7.1%</td>
</tr>
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*Phase 2 Study Completers at 24 Weeks*\(^*\)

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**Dopamine Drives the Reward System\(^1\)**

Food cues are associated with increased dopamine release in brain regions of the reward pathway

Repeated dopamine reward pathway stimulation can lead to:
- Compulsive food consumption
- Loss of food intake control
- Conditioned responses to food stimuli

Yellow/green associated with lower density of available dopamine receptors due to increased dopamine release.

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**Naltrexone and Bupropion Synergistically Reduced Food Intake in Mice When Administered in the Mesolimbic Reward System\(^1\)**

In fasted mice, injection of naltrexone + bupropion into the VTA significantly reduced 1-hour food intake\(^*\)

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**Naltrexone and Bupropion in the Mesolimbic Reward System**

- Bupropion HCl
  - Indicated as an aid to smoking cessation
  - Stimulates POMC cells, which suppress appetite
- Naltrexone HCl
  - Indicated for the treatment of alcohol dependence and for prevention of relapse to opioid dependence
- Blocks β-endorphin negative feedback loop on POMC neurons, which further contributes to appetite suppression
Summary

• The brain plays a pivotal role in weight regulation
• The hypothalamic hunger system and the mesolimbic reward system are key centres controlling food intake
• Naltrexone and bupropion exert effects on both the hypothalamic hunger system and mesolimbic reward system, resulting in altered eating behaviour and weight loss