Neurohormonal Mechanisms of Obesity – The Role of the Brain

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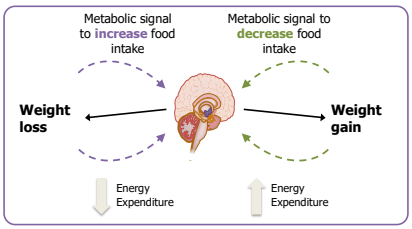
Disclosures

- Consultant to iNova
- Consultant to Novo Nordisk
- Research funding from Novo Nordisk

Homeostatic Regulation of Set Point Body Weight[1]

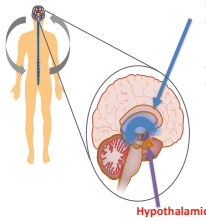
A homeostatic weight regulatory system prevents deviation from a body weight set point



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

1. Yu YH et al. *Obes Rev.* 2015;16:234-247.

Two Centers of the Brain Are Involved in Food Intake and Energy Balance[1,2,3,4]



Mesolimbic Reward System[1,2]

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

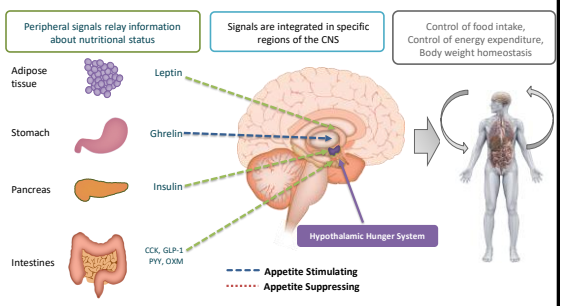
Mesolimbic reward system can override the hypothalamic hunger system increasing the consumption of highly palatable foods[3]

Hypothalamic Hunger System[4]

- Detection and integration of peripheral signals of hunger, fullness, and fat stores to **modulate feeding behavior** and **energy balance** (eg, appetite suppression by leptin [adipose], appetite stimulation by ghrelin [stomach]).
- Signals can be altered in obesity (eg, leptin resistance)

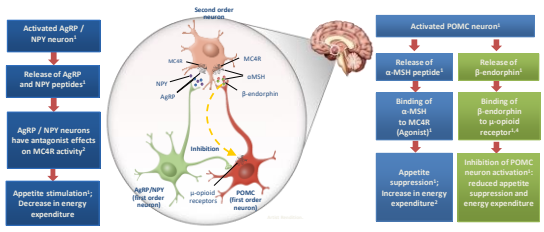
1. Morton GJ et al. *Nature.* 2006;443:289-295. **2.** Billes SK et al. *Pharmacol Res.* 2014;84:1-11.
3. Volkow ND et al. *Obes Rev.* 2013;14:2-18. **4.** Yu JH et al. *Diabetes Metab J.* 2012;36:391-398.

Hypothalamic Hunger System Within the CNS Integrates Complex Peripheral Signals to Regulate Body Weight Homeostasis[1,2]



CCK=cholecystokinin; CNS=central nervous system; GLP-1=glucagon-like peptide 1; OXM=oxyntomodulin; PYY=peptide YY.
1. Mendieta-Zerón H et al. *Gen Comp Endocrinol.* 2008;155:481-495.
2. Lean MEJ et al. Int J Obes (Lond). 2016;40:622-632

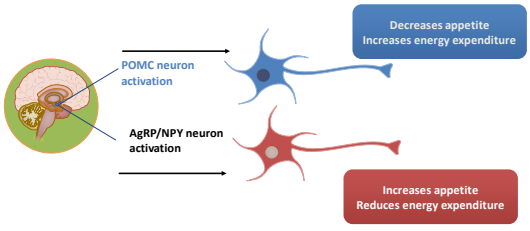
Peptides Modulate Appetite and Energy Expenditure in the Arcuate Nucleus of the Hypothalamus[1-4]



AgRP=agouti-related protein; NPY=neuropeptide Y; MC4R=melanocortin 4 receptor; POMC=propiomelanocortin; α-MSH, α-melanocyte-stimulating hormone.
1. Stahl SM. In: *Stahl's Essential Psychopharmacology.* 4th ed. New York, NY: Cambridge University Press; 2013:537-575.
2. Yu JH et al. *Diabetes Metab J.* 2012;36(6):391-398.
3. Mendieta-Zerón H et al. *Gen Comp Endocrinol.* 2008;155:481-495.
4. Cone RD. *Nat Neurosci.* 2005;8(5):571-578.

The hypothalamic hunger system [1,2]

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



AgRP=agouti-related protein; NPY=neuropeptide Y; POMC=proopiomelanocortin.
1. Yu JH et al. *Diabetes Metab J.* 2012;36:391-398. 2. Dietrich MO et al. *Nat Rev Drug Discov.* 2012;11:676-691.

POMC neurons' role in hunger[1]

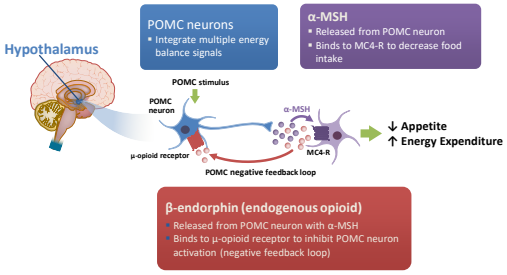


Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.
α-MSH=α-melanocyte-stimulating hormone; MC4-R=melanocortin-4 receptor; POMC=proopiomelanocortin.
1. Billes SK et al. *Pharmacol Res.* 2014;84:1-11.

- 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[1]

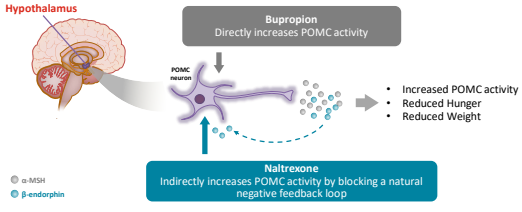


Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.
MSH=melanocyte-stimulating hormone; POMC=pro-opiomelanocortin.
1. Billes SK et al. *Pharmacol Res.* 2014;84:1-11.

In Vitro POMC Neuron Activity[1]

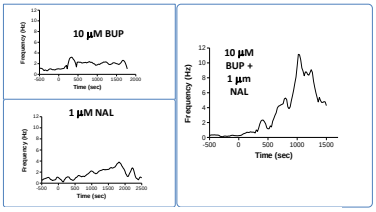
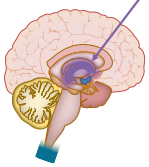


Fig. 2. Effect of naltrexone and bupropion on activity of POMC cells. Application of bupropion (10 μmol/L), naltrexone (1 μmol/L) and naltrexone (1 μmol/L) + bupropion (10 μmol/L) to mouse hypothalamic slices containing arcuate POMC-EGFP cells. Combined application of naltrexone and bupropion was associated with a transient increase POMC cell activity. Shading indicates duration of drug application.
Figure adapted from Greenway et al. [117]. Author retains copyright.

1. Billes SK et al 2014. Pharmacological research 84, 1-11.

Mesolimbic Reward System



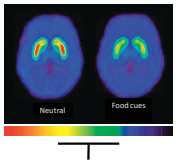
Mesolimbic Reward System

- Center of the brain that mediates the **motivation, reward, desire, pleasure,** and **reinforcement** associated with activities needed for survival (eg, eating, reproduction)[1,2]
- Centers of dopamine and opioid receptor signaling[1,3]
- The Mesolimbic Reward System evolved to respond to high fat, high sugar foods to aid survival[1,3,4]
- Associated with reward-based eating behavior and cravings in food-plentiful environment[1,4]

1. Billes SK et al. *Pharmacol Res*. 2014;84:1-11. 2. Zheng H et al. *Int J Obes (Lond)*. 2009;33:S8-S13. 2. Morton GJ et al. *Nature*. 2006;443:289-295. 3. Volkow ND et al. *Obes Rev*. 2013;14:2-18.

Dopamine Drives the Reward System[1]

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



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

Repeated dopamine reward pathway stimulation can lead to:

- Compulsive food consumption
- Loss of food intake control
- Conditioned responses to food stimuli

Image reprinted from Volkow ND, et al,[1] by permission of the Royal Society.
1. Volkow ND et al. *Philos Trans R Soc Lond B Biol Sci*. 2008;363:3191-3200.

Evidence Supports Altered Mesolimbic Reward System Activation in Patients With Obesity

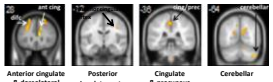
Fasted/Hungry State

Individuals with obesity have greater reward system activation in response to pictures of high-calorie foods compared with lean individuals[1*]

Nucleus accumbens

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[2*]



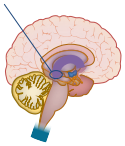
Anterior cingulate & dorsolateral frontal cortex | Posterior cingulate cortex | Cingulate & precuneus | Cerebellar

*Images represent subtracted differences in fMRI activation in response to food cues between obese and lean individuals (obese>lean).

Figure on left adapted from Stoeckel et al. [1] © 2008, with permission from Elsevier. Figure on right adapted from Puzziferri et al.[2] © 2016 The Obesity Society, with permission from John Wiley and Sons.
Ant cing=anterior cingulate; Cing=cingulate; Dlfc=dorsolateral frontal cortex; fMRI=functional magnetic resonance imaging; NAc=nucleus accumbens; Prec=precuneus.
1. Stoeckel LE et al. *NeuroImage*. 2008;41:636-647. 2. Puzziferri N et al. *Obesity*. 2014;24:829-836.

Naltrexone and Bupropion Synergistically Reduced Food Intake in Mice When Administered in the Mesolimbic Reward System[1]

Ventral Tegmental Area (VTA) of Mesolimbic Reward System



In fasted mice, injection of naltrexone + bupropion into the VTA significantly reduced 1-hour food intake[a]

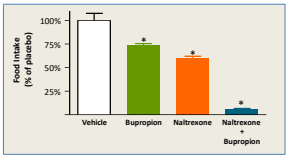
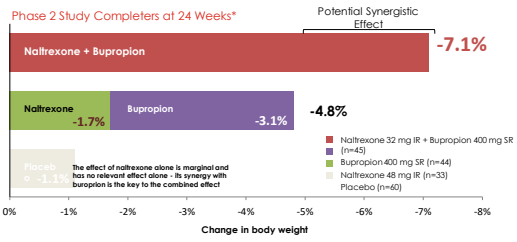


Figure on right adapted from Billes et al,[1] © 2014, with permission from Elsevier.
*P<0.01 compared to vehicle.
[a]One-hour food intake following intra-ventral tegmental area injection of naltrexone 1 µg, bupropion 1 µg, or naltrexone 1 µg/bupropion 1 µg in 16-hour fasted mice (n=8/group). Data are mean (standard deviation).
1. Billes SK et al. *Pharmacol Res*. 2014;84:1-11.

Combination Naltrexone + Bupropion Resulted in Greater Weight Loss vs the Individual Components[1]



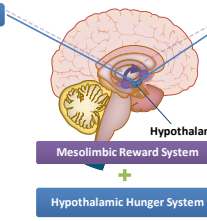
*Data are for Completer Population.
IR=immediate release; SR=sustained release.
1. Greenway FL et al. *J Clin Endocrin Metab*. 2009;94:4898-4906.

Naltrexone and Bupropion in the Mesolimbic Reward System

Bupropion HCl

Indicated as an aid to **smoking cessation**

Stimulates **POMC cells**, which suppresses 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

Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.
POMC=pro-opiomelanocortin.
1. Billes SK, et al. *Pharmacol Res*. 2014;84:1-11.

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