Neural Integration of Metabolic, Cognitive & Emotional signals in the Control of Ingestive Behavior

Hans-Rudi Berthoud

Neurobiology of Nutrition Laboratory
Pennington Biomedical Research Center
Louisiana State University System

IASO
Hot Topics Mental Health & Obesity
June 26-27, 2011
Toronto, Canada
Fundamentals of Energy Balance Regulation

NPY/AgRP Neurons Are Essential for Feeding in Adult Mice but Can Be Ablated in Neonates
Luquet S et al., Science 2005
Wu et al., Neuron 2009

Rapid, reversible activation of AgRP neurons drives feeding behavior in mice
Krashes MJ et al., J Clin Invest 2011

Diphteria-Toxin

![Graph showing licks and body weight over days with Diphteria-Toxin treatment.](image)

Internal Milieu

IASO Toronto
What causes obesity?

1. Defective homeostatic regulation 
   (e.g. leptin-deficiency, MC4R mutation, defective satiety mechanisms, 
   low sympathetic tone, brown fat-deficiency, and/or hypothalamic injury)

2. Defective hedonic/cognitive processing 
   and reward functions  
   (e.g. hypersensitivity to food 
   cues and palatable foods, altered dopamine-signaling)

3. Defective inhibitory control 
   (e.g. high impulsivity and/or lack of delayed discounting ability)

4. Environment & Lifestyle  
   (nothing wrong with physiology) 
   Simple adaptive response to environment of plenty
“Normal” upper level of body weight/adiposity is not or no longer defended in prone individuals

“Thrifty Gene”- Environment Mismatch Theory (Adaptively “thrifty” genes selected for fuel-efficiency) (Prentice, 2005, and many others)

“Random Drift” Set-Point Theory (Non-adaptive, random upward drift due to lack of predators) (Speakman, 2008)

Over-stimulation of cognitive and emotive processes “overpowers” the weak defense of upper body weight limits

IASO Toronto
External Stimuli
Unconditioned or Conditioned

- Sight
- Smell
- Taste

Representations of food & Reward expectancy
Orbitofrontal, cingulate, insular

Learning
Hippocampal complex

BLA
CeA

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Reward Calculation
N. Accumbens
Vent. Pall, VTA
Lateral Hypothalamus

Executive Control
Decision Making
SMA
Motor Cortex

Dorsolateral Prefrontal

Conscious & unconscious actions

Integrative Energy Sensor
& Response Allocator
Hypothalamus and Brainstem

Circulating Signals
of Energy Availability
(e.g. leptin, ghrelin, glucose)

Primary Afferents
(Vagal & spinal)

Metabolism

Unconscious behavioral, autonomic and endocrine control

IASO Toronto
Neuro-economics: making optimal decisions

Hare et al., J Neurosci, 2008

**Decision Value**
Net value of taking different actions

**Goal Value**
Predicted reward from projected outcomes

**Prediction Error**
Deviations from previous reward expectations

Orbitofrontal cortex
Vent. Striatum N. Accumbens

IASO Toronto
Interactions

Mental Health

External Stimuli
- Sight
- Smell
- Taste

Representations of food & Reward expectancy
Orbitofrontal, cingulate, insular

Executive Control
Decision Making
Dorsolateral Prefrontal

SMA
Motor Cortex

Conscious & unconscious actions

Interactions

Integrative Energy Sensor
& Response Allocator
Hypothalamus and Brainstem

Circulation of Energy
(e.g. leptin)

Unconscious behavioral, autonomic and endocrine control

Metabolism
Depression & Obesity: a bidirectional relationship

Koponen et al., 2008: Non-depressed women and men with metabolic syndrome at baseline were twice as likely to have depressive symptoms after 7 years.

Vanhala et al., 2009: Depressed women without the metabolic syndrome at baseline were more than twice as likely to develop the metabolic syndrome after 7 years.
Top-down modulation of eating by cognitive and emotional processes

Representations of food & Reward expectancy

Orbitofrontal, cingulate, insular

Executive Control
Decision Making

SMA
Motor Cortex

Dorsolateral Prefrontal

Conscious & unconscious actions

Conditioned Eating

Integrative Energy Sensor & Response Allocator
Hypothalamus and Brainstem

Circulating Signals
of Energy Availability
(e.g. leptin, ghrelin, glucose)

Primary Afferents
(Vagal & spinal)

Metabolism

Unconscious behavioral, autonomic and endocrine control

External Stimuli
Unconditioned or Conditioned

Sight
Smell
Taste

Learning
Hippocampal complex

BLA
CeA

Habits
Thalamus
Subst. Nigra
Dors. Striat

Reward Calculation
N. Accumbens
Vent. Palli, VTA
Lateral Hypothalamus
Conditioned Food Intake
Eating in the absence of metabolic need

Research with subliminal stimuli suggests:
Expected rewards can energize behavior without the need for the subject’s awareness

Pessiglione et al., Science 2007
Aarts et al., Science, 2008
Cognitive control of sensory perception and pleasantness

Expensive wines taste better!

Plassmann et al. PNAS 2008

Top-down cognitive processes encoding flavor expectancies are integrated in the medial orbitofrontal cortex
Unconscious determinants of free decisions in the human brain

Soon et al., J Neurosci, 2008

Decoding the outcome of decisions before and after they reached awareness

“When the subject’s decision reached awareness, it had been influenced by unconscious brain activity for up to 10 s

(skin conductance preceding risky decisions, Bechara et al., Science, 1997)
Top-down modulation of eating by cognitive and emotional processes

A fronto-parietal (inf. front. & pre-suppl. motor area) "Inhibition Network" is influenced by both conscious and unconscious information

Van Gaal et al., J Neurosci, 2010

Inhibition of inappropriate actions

Unconscious behavioral, autonomic and endocrine control

Metabolism

IASO Toronto
Bottom-up modulation of cortico-limbic functions by metabolic signals

Modulation by circulating hormones

Circulating Signals of Energy Availability (leptin, ghrelin, glucose)

Integrative Energy Sensor & Response Allocator
Hypothalamus and Brainstem

Primary Afferents (Vagal & spinal)

Metabolism

Unconscious behavioral, autonomic and endocrine control

Conscious & unconscious actions

External Stimuli
Unconditioned or Conditioned

Sight
Smell
Taste

Representations of food & Reward expectancy
Orbitofrontal, cingulate, insular

Learning
Hippocampal complex

Executive Control
Decision Making
SMA
Motor Cortex

Dorsolateral Prefrontal

Habits
Thalamus

Reward Calculation
N. Accumbens
Vent. Pall, VTA
Lateral Hypothalamus
Ghrelin modulates neural activity in cortico-limbic structures evoked by food pictures

Malik et al., Cell Metabolism, 2008
Ghrelin mediates stress-induced food-reward behavior in mice

Chuang, Zigman et al., 2011

Chronic Social Defeat Stress

Ghrelin attenuates stress-associated depression-like behavior

Prolonged psychosocial stress

β-adrenergic stimulation via SNS

Ghrelin

Catecholaminergic neurons

Conditioned place preference for high-fat diet

A 

WT

Knockout

B

Body weight

C

D

No compensation by eating more chow

Wild-type GHSR-null

Wild-type GHSR-null

Wild-type GHSR-null

Wild-type GHSR-null

Wild-type GHSR-null

Wild-type GHSR-null

Wild-type GHSR-null
Bottom-up modulation of cortico-limbic functions by metabolic signals

Leptin, Insulin, GLP-1

Modulation by “Gut Feeling”

How do you feel? and the “Sentient self”

The anterior insula & human awareness

AD Craig, Nat Rev Neuroscience 2010
A significant fat-by-emotion interaction effect on the BOLD signal was found: fatty acid attenuates the effect of sad emotion compared with saline.
Ingestion of *Lactobacillus* regulates emotional behavior and GABA receptor in the mouse via the vagus nerve

Bravo JA, Cryan JF et al., *PNAS*, 2011

The emerging field of

**Microbiota → Gut → Brain axis**

Search for microbes with psychotropic properties
Conclusions

- The neural systems mediating energy balance are complex, distributed, and redundant.

- A homeostatic regulator is organized around an “ancient” paraventricular core including hypothalamus and brainstem.

- A hedonic decision making system is organized around cortico-limbic systems.

- The rules of interaction between these systems are likely to be important for understanding common obesity and its relationship with mental health.
Neurobiology of Nutrition Laboratory

Pennington Faculty & Staff
Chris Morrison
Heike Münzberg
Brenda Richards
Jennifer Dowden
Don Ingram
Jianping Ye
Zheng Hao

Outside Collaborators
University of Calgary
David Sigalet
Henry Koopmans
Harvard University
Nicholas Stylopoulos
Lee Kaplan

NIDDK

Andrew Shin
Laurel Patterson
Natalie Lenard
Katherine Stewart
Huiyuan Zheng
Leigh Townsend
Conclusions
Circulating Signals of Energy Availability (e.g. leptin, ghrelin, glucose)

Representations of food & Reward expectancy
Orbitofrontal, cingulate, insular

Executive Control
Decision Making
SMA → Motor Cortex

External Stimuli
Unconditioned or Conditioned

Integrative Energy Sensor & Response Allocator
Hypothalamus and Brainstem

Primary Afferents (Vagal & spinal)

Liver, AT Pancreas

Gut

Food Intake

Energy Expenditure
BMR, Thermogenesis, SPA, Exercise

Voluntary Exercise

Subconscious behavioral, autonomic, & endocrine control

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.

Sight

Smell

Taste

Interacting pathways

Voluntary behavioral control

Executive Control
Decision Making
SMA → Motor Cortex

Conscious voluntary behavioral control

Learning
Hippocampal complex

BLA
CeA

Reward Calculation
N. Accumbens
Vent. Pall., VTA
Lateral Hypothalamus

Habits
Thalamus
Subst. Nigra
Dors. Striat.
Fatty acid–induced gut-brain signaling attenuates neural and behavioral effects of sad emotion in humans

Lukas Van Oudenhove¹,², Shane McKie³, Daniel Lassman², Bilal Uddin², Peter Paine², Steven Coen⁴, Lloyd Gregory², Jan Tack¹ and Qasim Aziz ²,⁴

¹Translational Research Centre for Gastrointestinal Disorders, University of Leuven, Leuven, Belgium.
²Department of Gastrointestinal Sciences and
³Neuroscience and Psychiatry Unit,
University of Manchester, Manchester, United Kingdom.
⁴Wingate Institute for Neurogastroenterology, Queen Mary University, London, United Kingdom.

**Fig. 1** Effect of sad emotion and intragastric fatty acid on behavioral ratings. (A) Hunger. A significant main effect of emotion (increase of hunger during sad, decrease during neutral) and a significant fat-by-emotion interaction (effect of sad on hunger attenuated by fat) was found. **P < 0.01** compared with saline vehicle sad; ***P < 0.001** compared with vehicle sad, corrected for multiple comparisons. (B) Fullness. A significant main effect of emotion (smaller increase in fullness during sad compared with neutral) was found. ***P < 0.001** compared with neutral.
(C) Mood. A significant main effect of emotion and a significant fat-by-emotion interaction (attenuation of the effect of emotion induction by fat) was found. All pairwise differences were significant after correction for multiple comparisons, except for vehicle neutral compared with fat neutral (NS, $P = 0.13$). VAS, visual analog scale.
Total intake (oral + intragastric; ± SE) on CS+ and CS− one-bottle training days and two-bottle tests of CD36 KO and B6 WT mice during intragastric conditioning in experiment 1B. During training and the reinforced test (Rein), intake of the CS+ was paired with intragastric infusions of 5% Intralipid. During the nonreinforced test (NR), intake of the CS+ was paired with intragastric water infusions. CS− intake was always paired with intragastric water infusions. The two-bottle test data are based on 2-day averages. Numbers atop bars represent mean percent preference for CS+ solution.