Central regulation of appetite and food intake

Alessandro Laviano
“Food, from time immemorial, is part of the nurturing process, and “Bread the Staff of Life”, all that stuff ... so when you think of food, you think, well, if you can eat, you can get healthy”.

A woman who had cared for patients with cancer
Clues to the role of the hypothalamus in the regulation of food intake

Bernard Mohr (1840s): first clinical description of hypothalamic-pituitary injury resulting in obesity.
Eyjafjallajökull volcano, Iceland

Credit: R. Th. Sigurdsson/Arctic-Images.com
GOAT links dietary lipids with the endocrine control of energy balance

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Mitochondrial β-oxidation

Fatty acid synthesis $\rightarrow$

$\uparrow$ malonyl-CoA $\rightarrow$

$\downarrow$ food intake

Fatty acid oxidation $\rightarrow$

$\downarrow$ malonyl-CoA $\rightarrow$

$\uparrow$ food intake
Fig. 1. (A) Time allocation for different postures for 10 obese and 10 lean sedentary subjects

**Fig. 3.** Study 3. Effect of Orexin A in rLHA on time spent moving in young DIO, DR, and SD rats. 

- *P < 0.05 compared with DIO rats at each dose; #P < 0.05 and ##P < 0.005 compared with SD rats at each dose. Data represent means ± SE, N = 9 (DIO), 11 (DR), and 10 (SD). Please note different y-axes.
Melanocortin signaling in the CNS directly regulates circulating cholesterol

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5-HT$_{2C}$Rs expressed by pro-opiomelanocortin neurons regulate insulin sensitivity in liver

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Mice lacking 5-HT 2C receptors (5-HT$_{2C}$Rs) displayed hepatic insulin resistance, a phenotype normalized by re-expression of 5-HT$_{2C}$Rs only in pro-opiomelanocortin (POMC) neurons. 5-HT$_{2C}$R deficiency also abolished the anti-diabetic effects of meta-chlorophenylpiperazine (a 5-HT$_{2C}$R agonist); these effects were restored when 5-HT$_{2C}$Rs were re-expressed in POMC neurons. Our findings indicate that 5-HT$_{2C}$Rs expressed by POMC neurons are physiologically relevant regulators of insulin sensitivity and glucose homeostasis in the liver.
Peripheral tissue

Challenge $\rightarrow$ ↑ CK

vagus nerve

Brainstem

↑ ACh, NA, 5HT innervation

Hypothalamus

↑ POMC $\rightarrow$ CK

↓ NPY

↑ APP

↑ UCPs

↑ sympathetic outflow

↓ food intake

↑ catabolism

↑ energy expenditure

↓ MCoA $\leftarrow$ ↓ FA oxidation

↓ CPT1c


Molfino A et al. Nature Reviews Cancer 2009
Preliminary results

Non anorexic cancer patient
Preliminary results

Anorexic cancer patient
Increased systemic inflammatory response (IL-1β, TNF-α, IL-6, other cytokines)

Hypothalamus
Increased melanocortin signaling

- Weight loss
- Loss of lean body mass
- Increased energy expenditure

MC4-R antagonists

Second order neuron

IL1-R
POMC
AgRP/NPY

MC3-R

Arcuate nucleus

De Boer M & Marks DL. Trends Endocrinol Metab 2006
Conclusions

- Tight regulation of food intake is critical to preserve healthy status, and thus growth and reproduction.
- Regulation of food intake is centrally mediated and largely influenced by peripheral factors.
- Redundancy of nervous circuitries controlling food intake underlines the critical role of maintaining body weight.
- More recent data show that the hypothalamus not only control food intake and appetite, but energy homeostasis as well.
- Better understanding of the central control of energy homeostasis may provide new strategies to treat acute and chronic diseases.
Michelangelo Buonarroti (1475-1564)
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Nutrition in translation