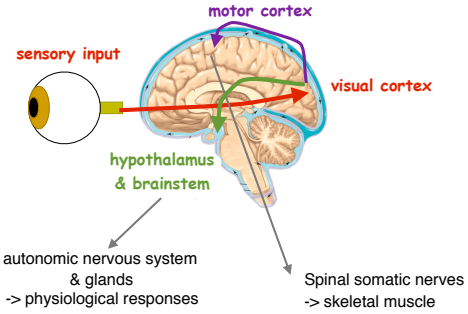
Control of Food Intake and Obesity

Chapter 16

General Scheme of CNS

receive sensory inputs, coordinate response of the organs & functions of the body

inputs:
see bear -> retina -> cranial nerve II (optic nerve) -> visual cortex
outputs:
-> motor cortex -> run away
-> hypothalamus -> stress hormone release -> mobilize glucose
-> brainstem -> increase heart rate, blood pressure, breathing



Visceral Neuraxis vs. Somatic Neuraxis

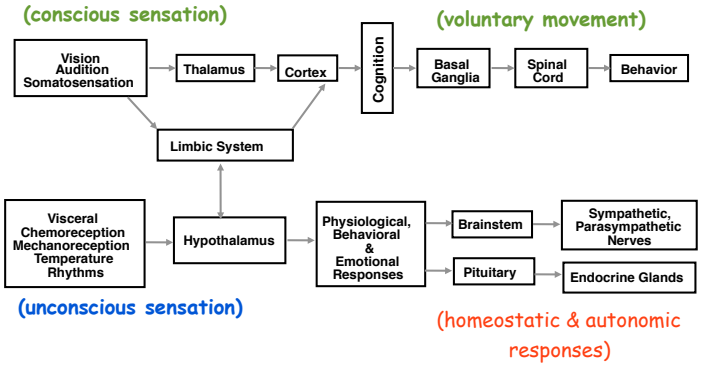
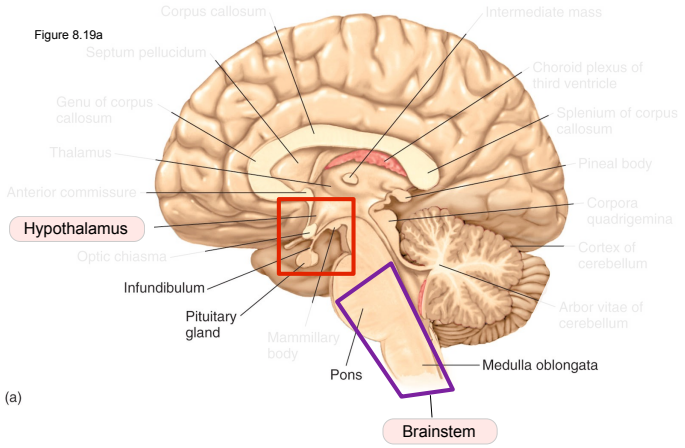
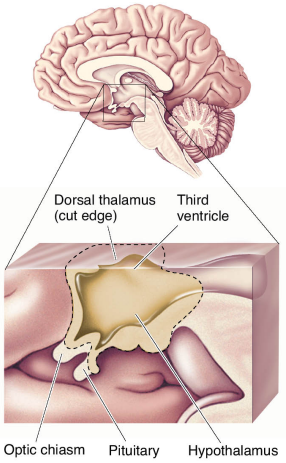


Figure 8.19a

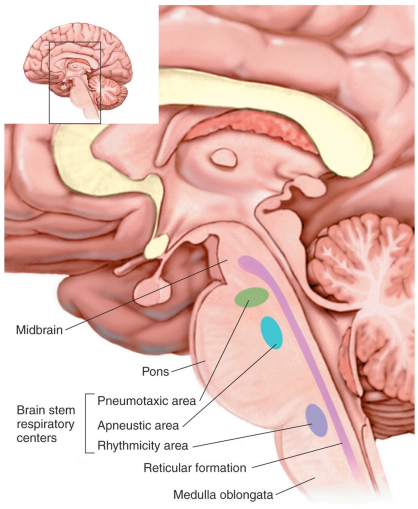


Hypothalamus



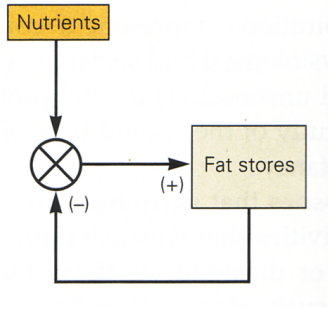
Wolters Kluwer

Figure 8.22



Feedback Regulation

High levels of regulated variable cause hypothalamus to downregulate behavior & physiology that drives variable up.



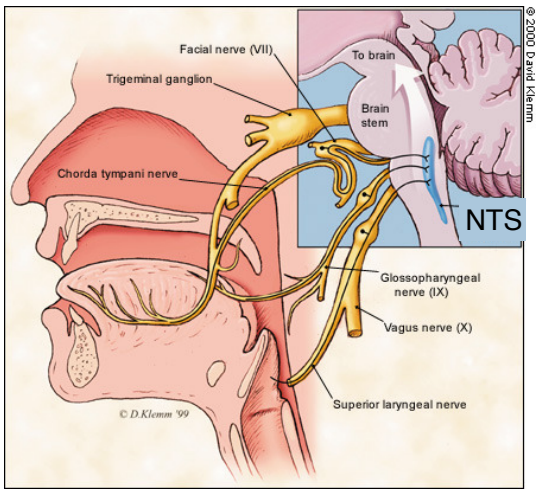
negative feedback loop balances positive input, no setpoint

Peripheral Mechanisms of Feeding Control

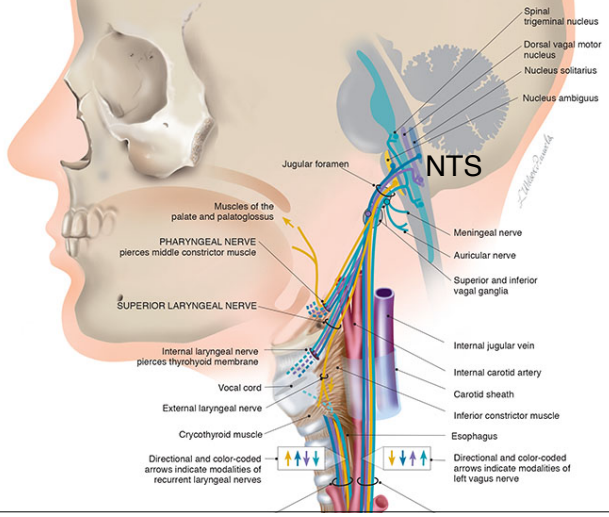
taste
–> positive feedback
–> gustatory nerves
–> rostral nucleus of the solitary tract
–> drives a brainstem “reflex” to eat

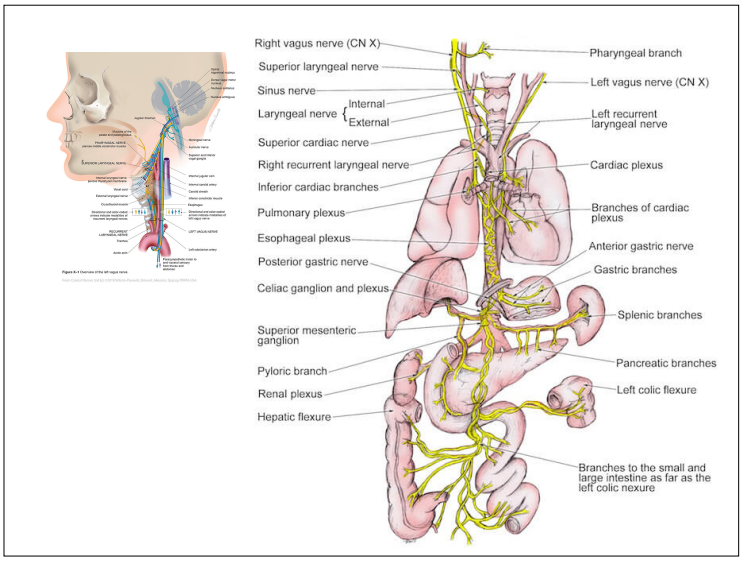
food
–> postingestive stimuli (gastric distention, CCK release and other hormones)
–> vagus nerve
–> caudal NTS
–> turn off response to taste

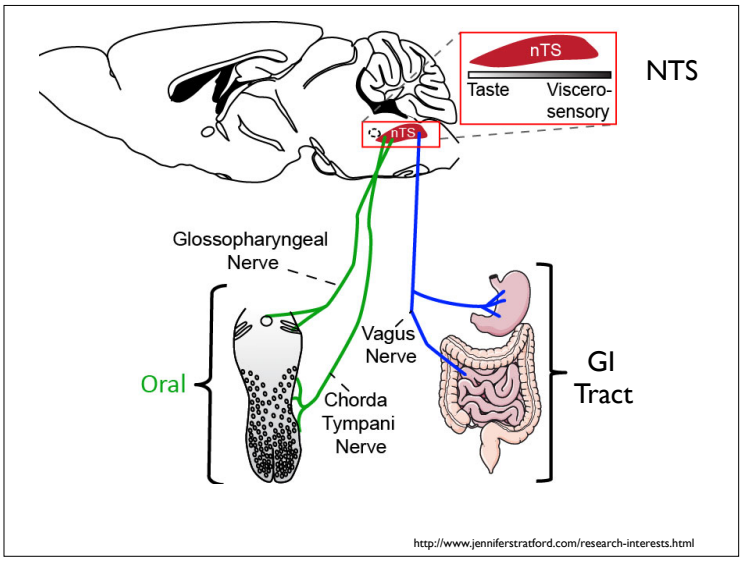
taste -> NTS (nucleus of the solitary tract)



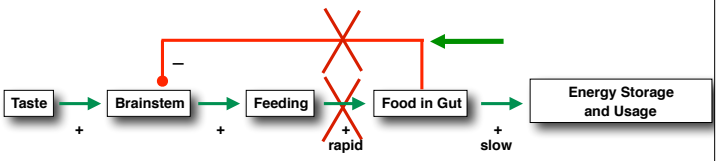
GI tract -> Vagus Nerve (cranial X) -> NTS







Short-term controls of Food Intake

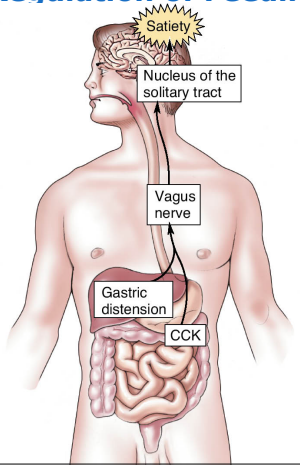


Meal Size is mediated by:

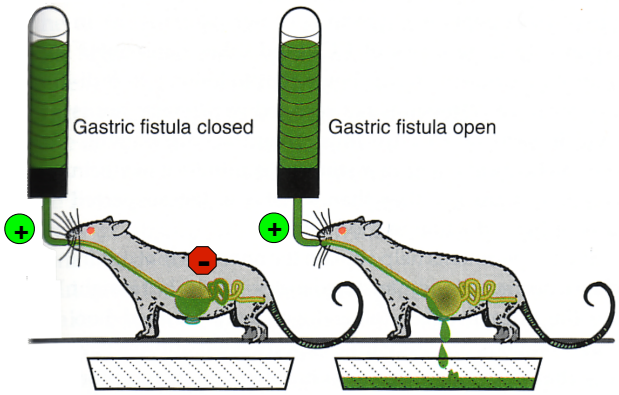
- **taste**
- **postingestive effect of food**
- **GI signals**
- **brainstem**

Model for Short-Term Regulation of Feeding

- Gastric: feeling full
  - Gastric distension signals brain via vagus nerve.
  - Works synergistically with CCK released in intestines in response to certain foods
  - Insulin also released by β cells of the pancreas—important in anabolism



Sham-Feeding dissociates positive from negative controls of feeding



Zigmond

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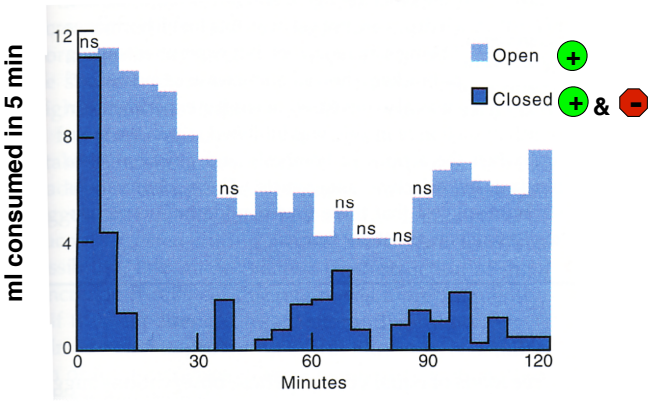


Zigmond

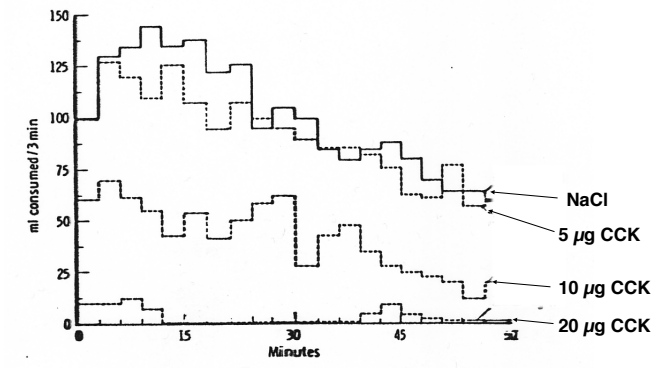
Can add back negative GI signals

Cholecystokinin (CCK):
8 amino acid peptide released from small intestine
release stimulated by fat, protein in gut

Physiological role of CCK:
contraction of gall bladder
stimulate pancreatic secretion

Neural role of CCK:
stimulate vagus nerve to terminate feeding

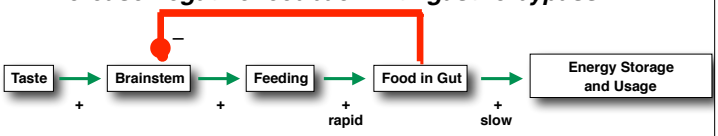
Can add back negative GI signals



Effects of slow intravenous infusions of cholecystokinin (CCK) on sham-feeding of liquid food in rhesus monkeys

Short-term controls of Food Intake

increase negative feedback with gastric bypass



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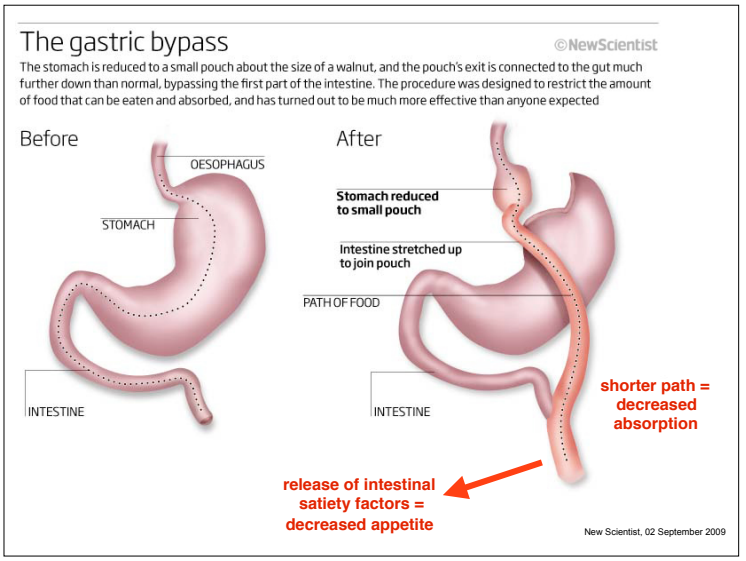
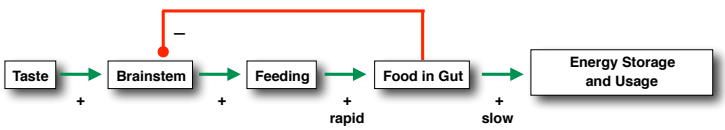


Short-term controls of feeding

CCK
gastric distension
osmotic concentration
etc
via blood, vagus, spinal afferents

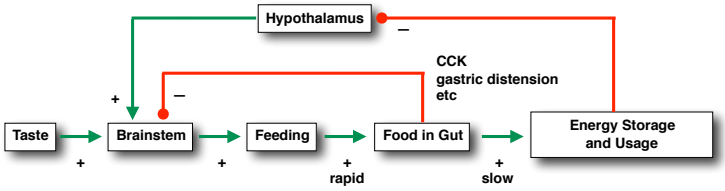


Clinical relevance:

Bulimics may be insensitive to CCK-> large meals
Case of brainstem tumor -> enhanced satiety
Obese family with mutant CCK receptors

Taste can overwhelm other controls...

Long-term negative feedback loop regulates body weight and adiposity



Brainstem feedback circuit alone cannot regulate body weight

big/small meals are compensated for by altering number or size of subsequent meals

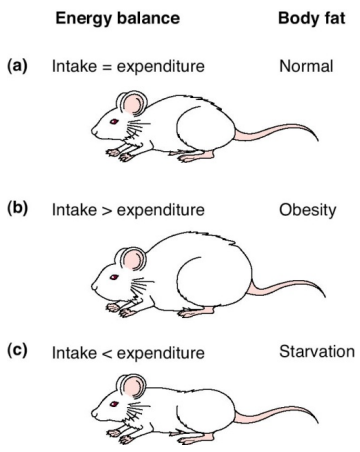
Hypothalamic feedback loop regulates overall energy balance and modulates brainstem circuit to change number/size of meals.

Obesity: a behavioral disorder

food in (+) –> fat mass –> metabolism, exercise (–)
energy intake –> energy store –> energy expenditure

Therefore, increased adiposity requires either decreased energy output or increased energy intake, or both.

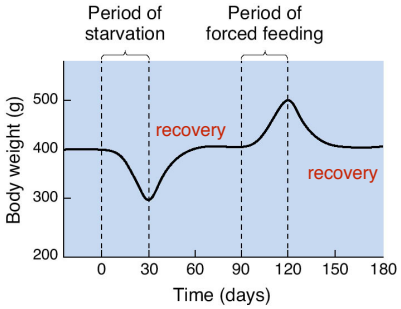
Energy expenditure plays a role:
- **metabolic contribution (i.e. body temp decreases)**
- **behavioral adjustments:**
  - **if underfed, fidgeting goes down.**
  - **if overfed, fidgeting goes up.**
  - **anorexia accompanied by increased exercise.**



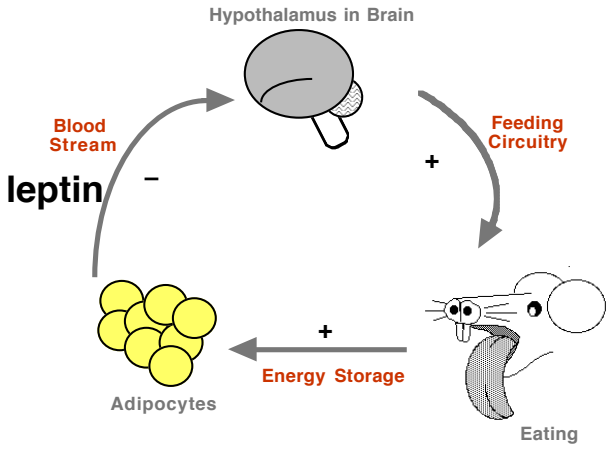
Body Fat and Food Consumption

How does body/brain maintain constant body weight after starvation or overfeeding?

- Lipostatic hypothesis
- Leptin
  - Regulates body mass
    - Decreases appetite
    - Increases energy expenditure
- Leptin depletion
  - Incites adaptive
  - responses to fight starvation



Feedback loops



Cloning of Leptin (leptos = thin) and receptor

Leptin = ~100 amino acid peptide hormone secreted by adipose tissue into the blood.

ob/ob mutation
–> extra stop codon terminates leptin transcript.
–> hypoleptinemia

db/db mutation
–> extra stop codon terminates leptin receptor
–> functional hypoleptinemia

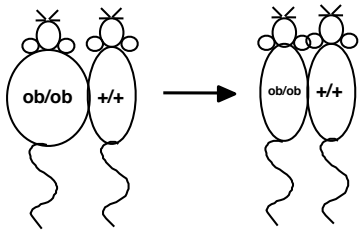
Obese Mutant Mice

ob/ob *obese* mouse
no leptin

db/db *diabetic* mouse
no leptin receptors

	Body mass	Adiposity
wildtype (+/+):	18 g	12 %
obese (ob/ob)	64 g	60 %

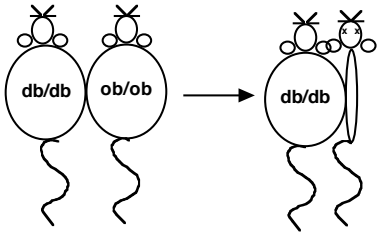
Parabiotic experiments with shared blood supply



wildtype blood
normalizes ob/ob

∴ wildtype has hormone that ob/ob is missing

Parabiotic experiments with shared blood supply



db/db blood
makes
ob/ob anorexic

∴ db/db has excess hormone that ob/ob is missing

hypoleptinemia and functional hypoleptinemia

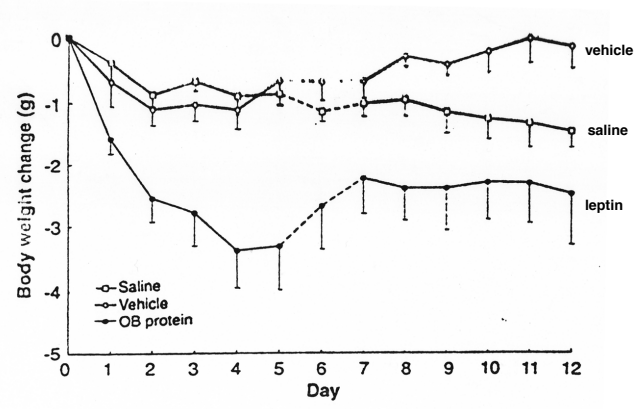
ob/ob is missing hormone supplied by wildtype mouse.

db/db is missing receptor, while increased fatmass overproduces hormone. This is same hormone that ob/ob is missing, because it makes ob/ob anorexic.

ob/ob: no leptin hormone, so can't produce negative feedback signal and keeps putting on fat.

db/db : no leptin receptors, so can't detect negative feedback signal, and keeps putting on fat.

Leptin decreases body weight in ob/ob mice



Do the Obese Rodent Models apply directly to human behavioral genetics?

1. Yes, there are occasional human mutants:
Anglo-Pakistani brothers lack leptin,
French sisters lack leptin receptors.

2. No, in fact leptin doesn't work well in humans.

3. Perhaps heterozygotes are common:
[female fa/+ rats are more susceptible to obesity when overfed.]

4. Polygenetic influences are clear.

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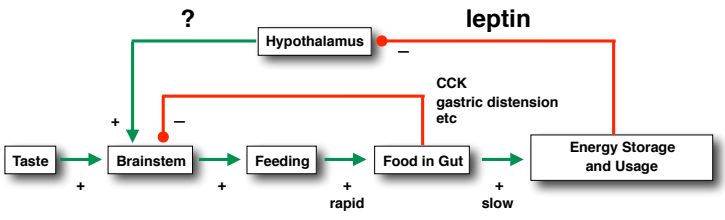
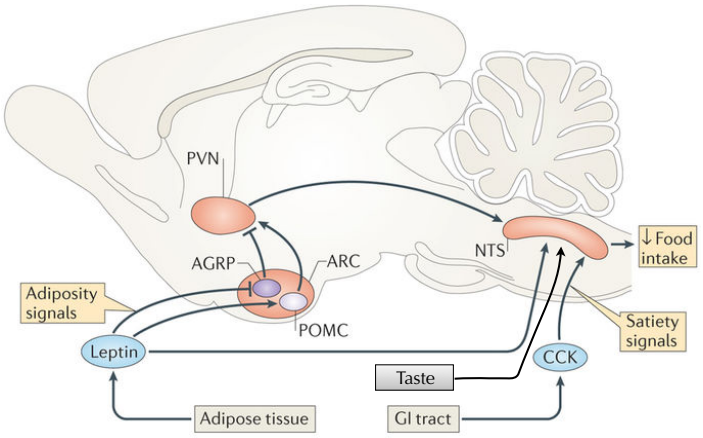
Eating and Body Weight determined by balance of positive and negative feedback signals

Loss of negative feedback can increase short- or long-term food intake





Schwartz 2014, Nature Reviews Neuroscience

Hypothalamic Mechanisms of Appetite

Satiety peptide (stimulated by leptin):

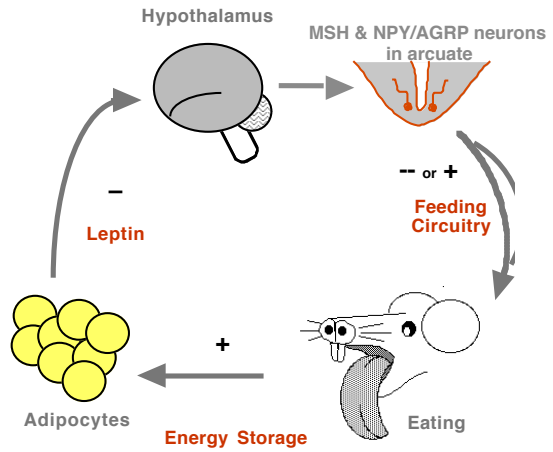
alpha-melanocyte stimulating hormone (a-MSH)
derived from POMC gene
activates melanocortin receptors

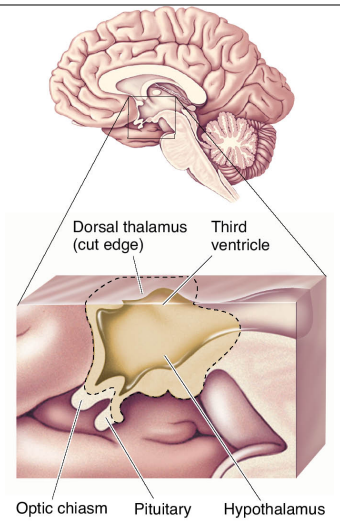
Orexigenic peptides (inhibited by leptin):

Neuropeptide Tyrosine (NPY)
Agouti-Gene Related Peptide (AGRP)
endogenous antagonist of aMSH at MC receptors

many other peptides; appealing but difficult targets

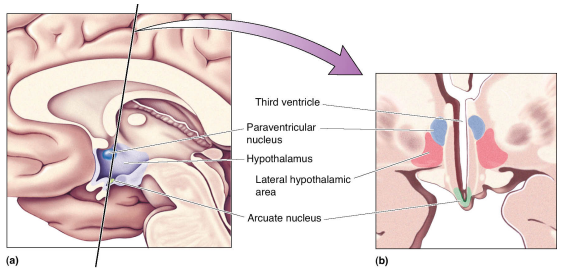
Feedback Loop: Leptin -> MSH, NPY/AGRP



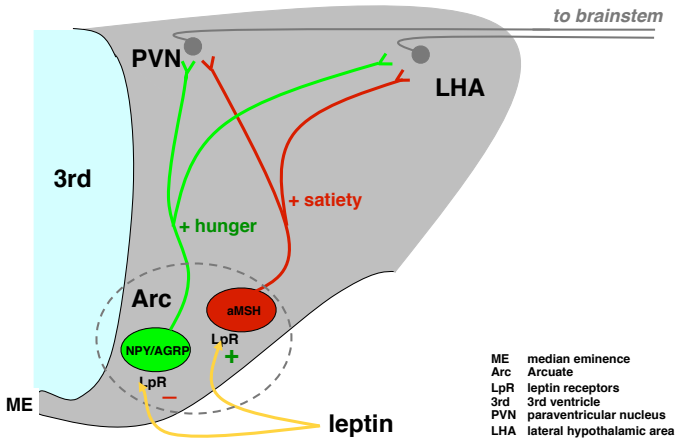


The Hypothalamus and Feeding—(cut.)

- Arcuate nucleus of hypothalamus important for the control of feeding



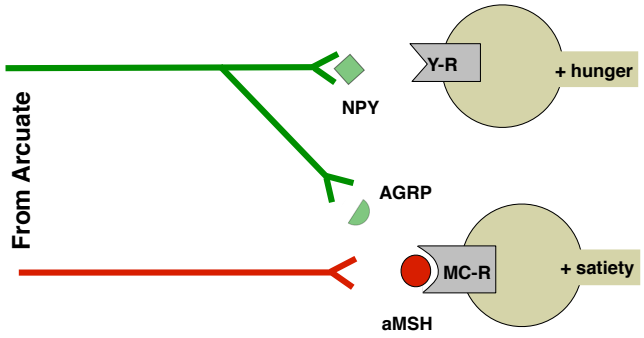
Plasma Leptin directly binds receptors on NPY/AGRP & aMSH neurons in the Arcuate



ME median eminence
Arc Arcuate
LpR leptin receptors
3rd 3rd ventricle
PVN paraventricular nucleus
LHA lateral hypothalamic area

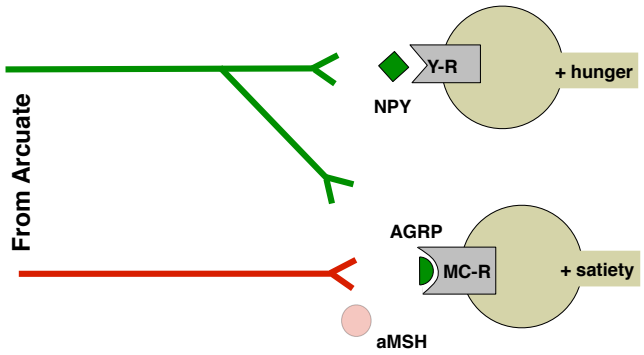
MSH & NPY have opposite effects: AGRP antagonizes MSH activity

Fed -> high Leptin -> high MSH, low NPY/AGRP -> small, infrequent meals

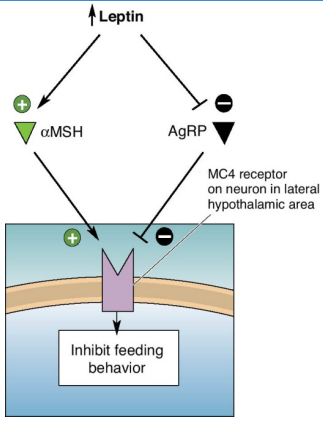


MSH & NPY have opposite effects: AGRP antagonizes MSH activity

Fast -> low Leptin -> low MSH, high NPY/AGRP -> large, frequent meals



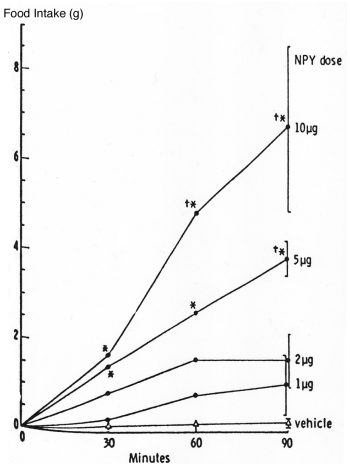
Competition for Activation of the MC4 Receptor



Wolters Kluwer

NPY –> Increased Food Intake

exogenous NPY injected into 3rd ventricle of normal rat causes prolonged eating.

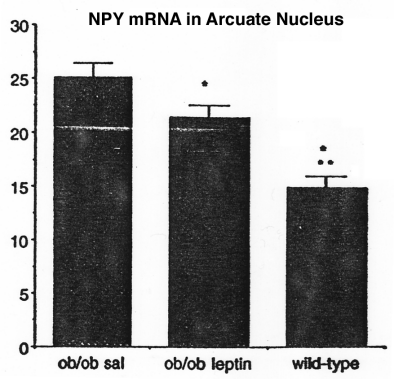


NPY is elevated in obese mutants

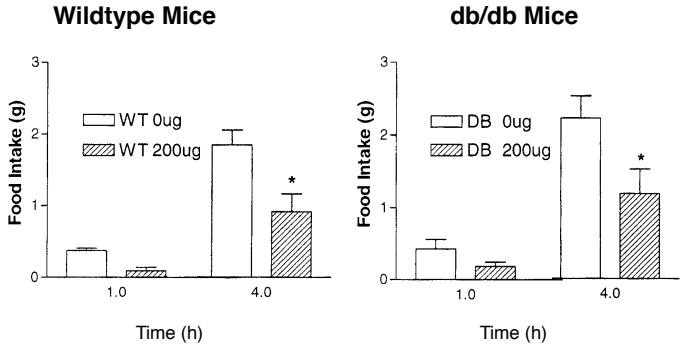
lack of leptin causes elevated NPY/AGRP

exogenous leptin decreases NPY/AGRP

(conversely, leptin increases aMSH)

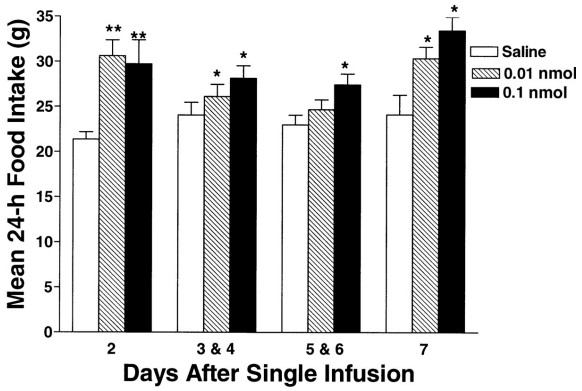


MSH agonist -> Decreased Food Intake



Benoit 2000 PMID 10777807

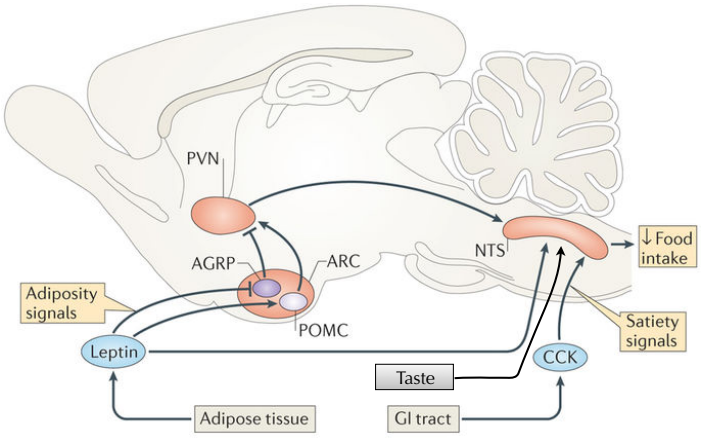
AGRP (MSH antagonist) -> Increased Food Intake



exogenous AGRP injected into 3rd ventricle of normal rat causes overeating for days.

Summary of Responses to Increased and Decreased Adiposity

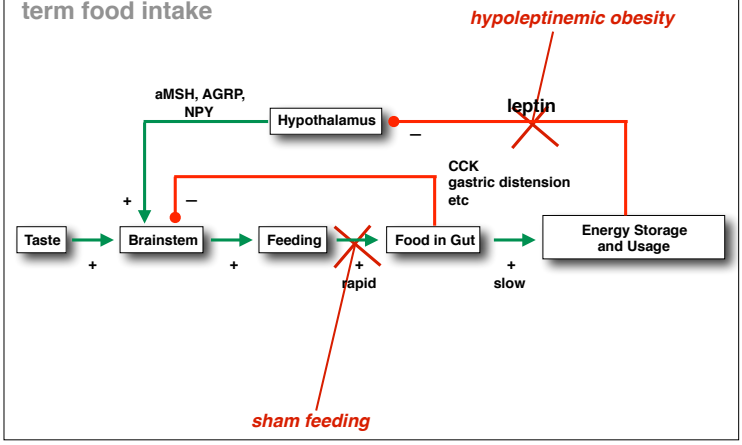
	Fat	Lean	
Blood leptin level	+	−	
αMSH/CART neuron activity	+	−	Arcuate nucleus response
NPY/AgRP neuron activity	−	+	
TSH and ACTH release	+	−	Humoral response
Sympathetic NS activity	+	−	Visceromotor response
Parasympathetic NS activity	−	+	
Feeding behavior	−	+	Somatic motor response



Schwartz 2014, Nature Reviews Neuroscience

Eating and Body Weight determined by balance of positive and negative feedback signals

Loss of negative feedback can increase short- or long-term food intake



Clinical Consequences of Feeding Circuits

How does taste, sugar, and fat change the balance between positive and negative feedback?

Palatable diets lead to dietary-induced obesity

Why are obese people “leptin resistant”?

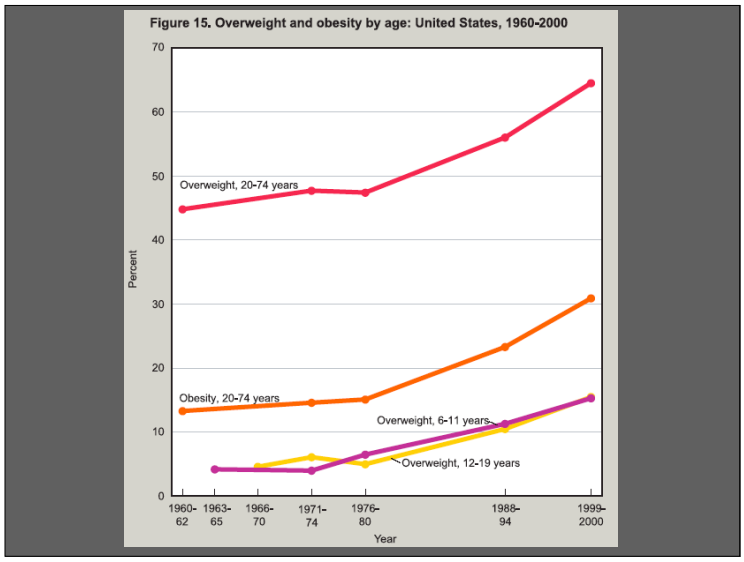
High circulating levels of leptin, but still they eat

How does uncoupling positive and negative signals lead to disordered eating behavior?

Bulimics separate eating from satiety/absorption

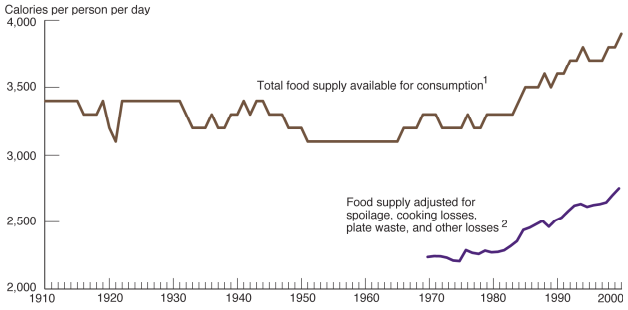
How does psychosocial stress alter hypothalamic response to peripheral signals?

Anorexics have zero leptin, but are not hungry



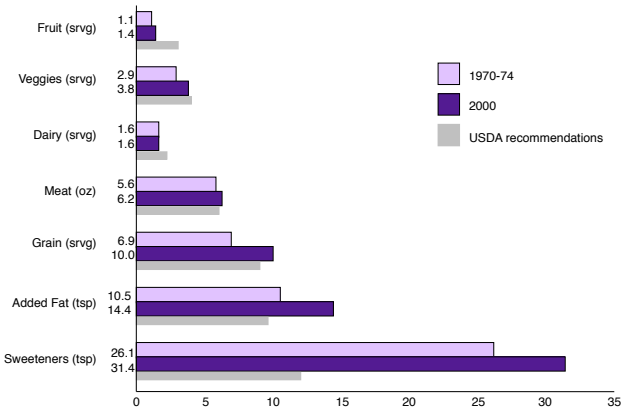
Caloric Intake parallels increase in Obesity

Figure 1—Calories From the U.S. Per Capita Food Supply, Adjusted for Losses, Increased 20 Percent Between 1982 and 2000



[1] Rounded to the nearest hundred.
[2] Not calculated for years before 1970.
Source: USDA's Center for Nutrition Policy and Promotion; USDA's Economic Research Service. Food Review Winter 2002

Intake is tilted towards highly palatable fat & sugar



USDA Economic Research Service
Food Review Winter 2002

Rise in "Food Away From Home" parallels increase in caloric intake

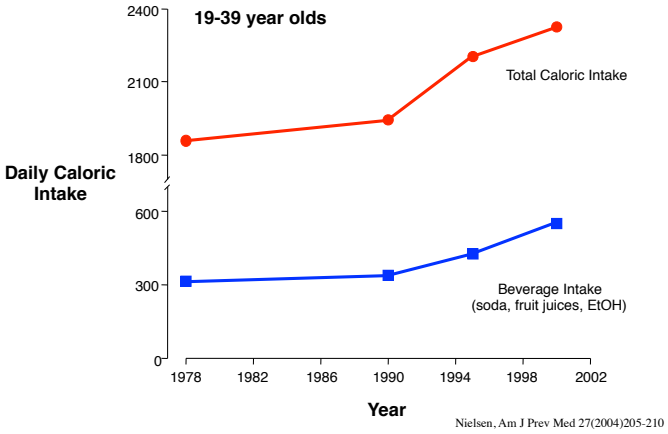
Food away from home, from 70s to 90s:

25% to 45% of total food spending

18% to 34% of total calories

USDA Economic Research, Lin et al., AG Bull 750, 1999

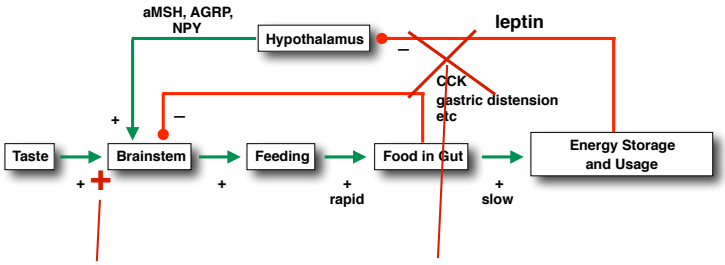
Beverage Intake accounts for increase in Caloric Sweetener Consumption?



Nielsen, Am J Prev Med 27(2004)205-210

Causes of Diet-induced Obesity

Tastes great vs. less filling?



sweet & fat fast food provides overwhelming positive feedback?

modern diet (e.g. sweet beverages) does not provide as much negative feedback?

Feeding and Obesity Conclusions

In the short-term, meal size is controlled by a taste-postingestive feedback system

CCK and the vagus nerve signal that food is in gut, before it is actually absorbed

Long-term adiposity is controlled by a hypothalamic feedback circuit

Leptin signals the accumulation of fat; leptin's absence signals the need to eat

Feeding is driven by hypothalamic neuropeptides regulated by leptin