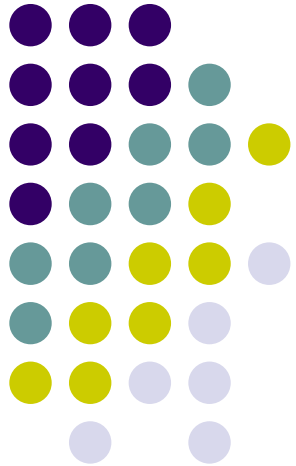
Verzehrsregulation

Wolfgang Langhans

Institut für Lebensmittelwissenschaft,
Ernährung und Gesundheit

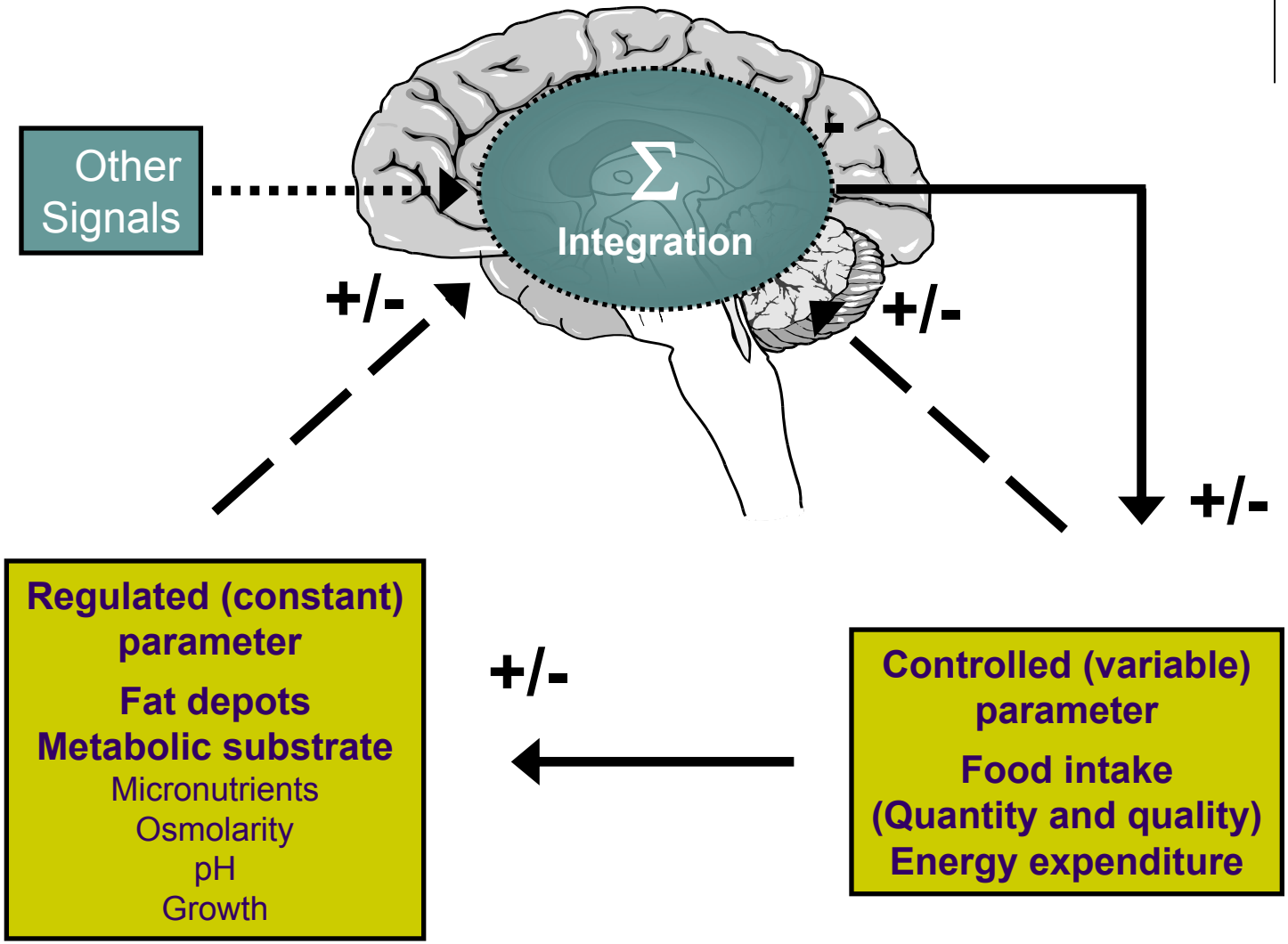
ETH-Zürich



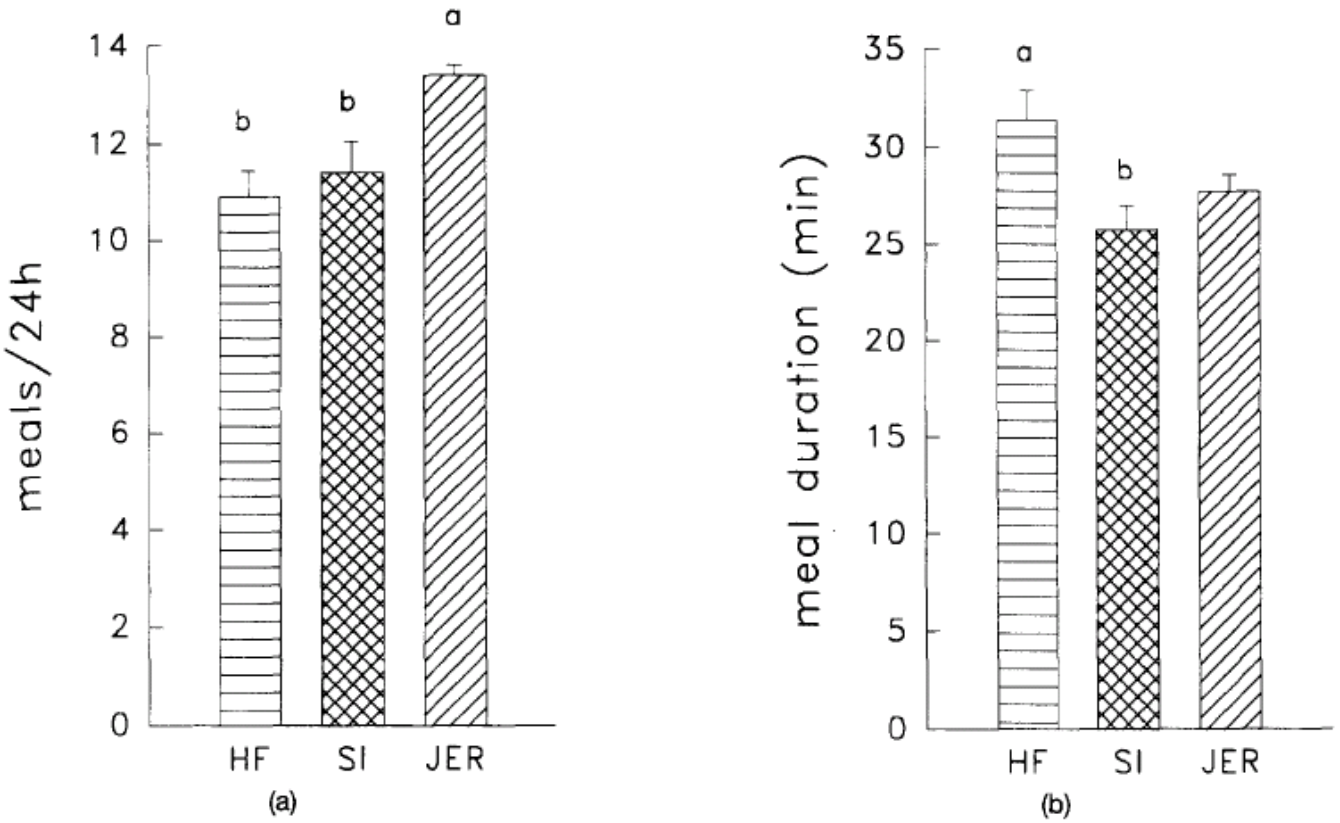
Verzehrsregulation

- **Allgemeines**
- Steuerung von Mahlzeitgrösse und -frequenz
- Adipositassignale
- Zentralnervöse Mechanismen
- Äussere und innere Faktoren

Energy balance and food intake

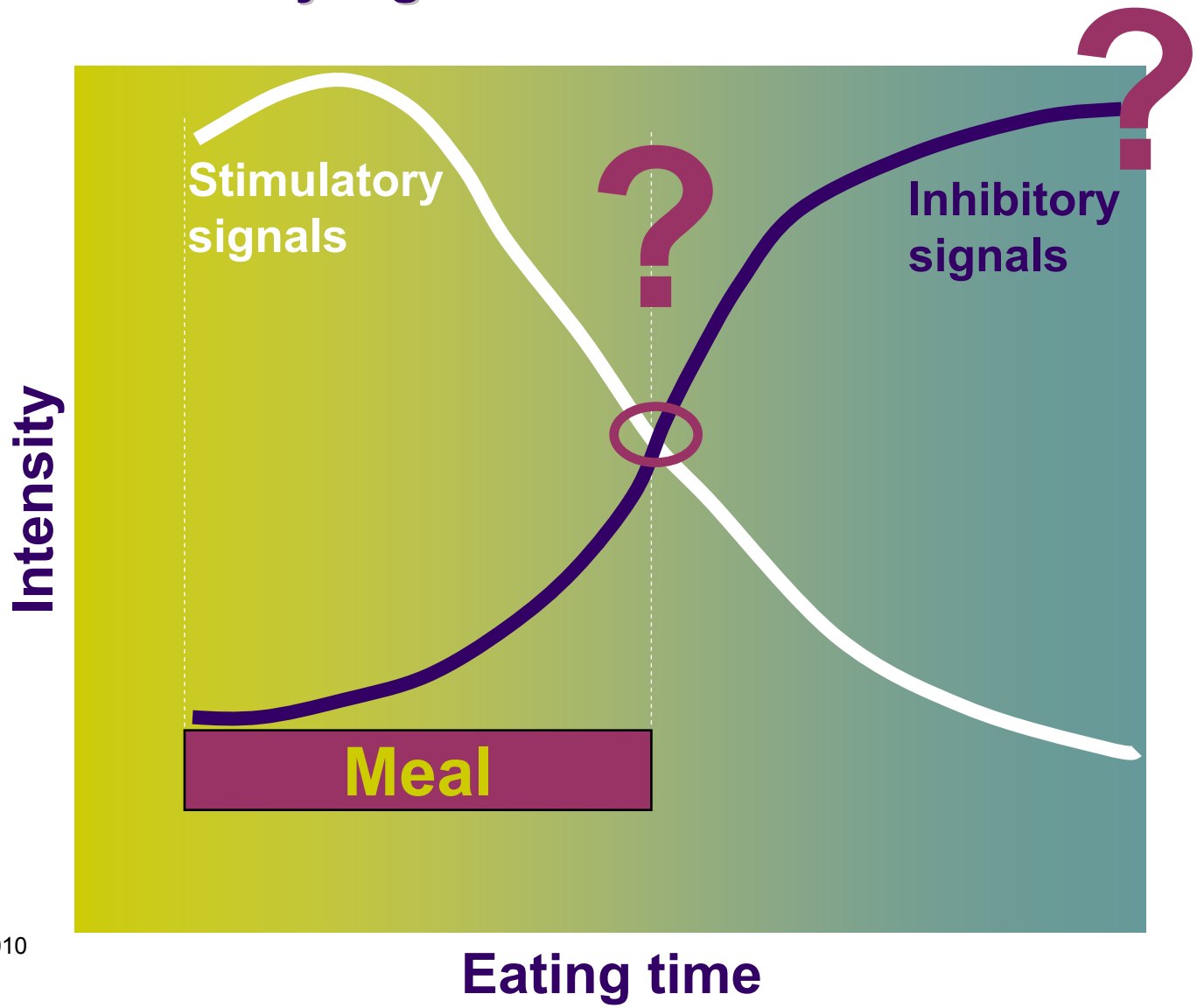


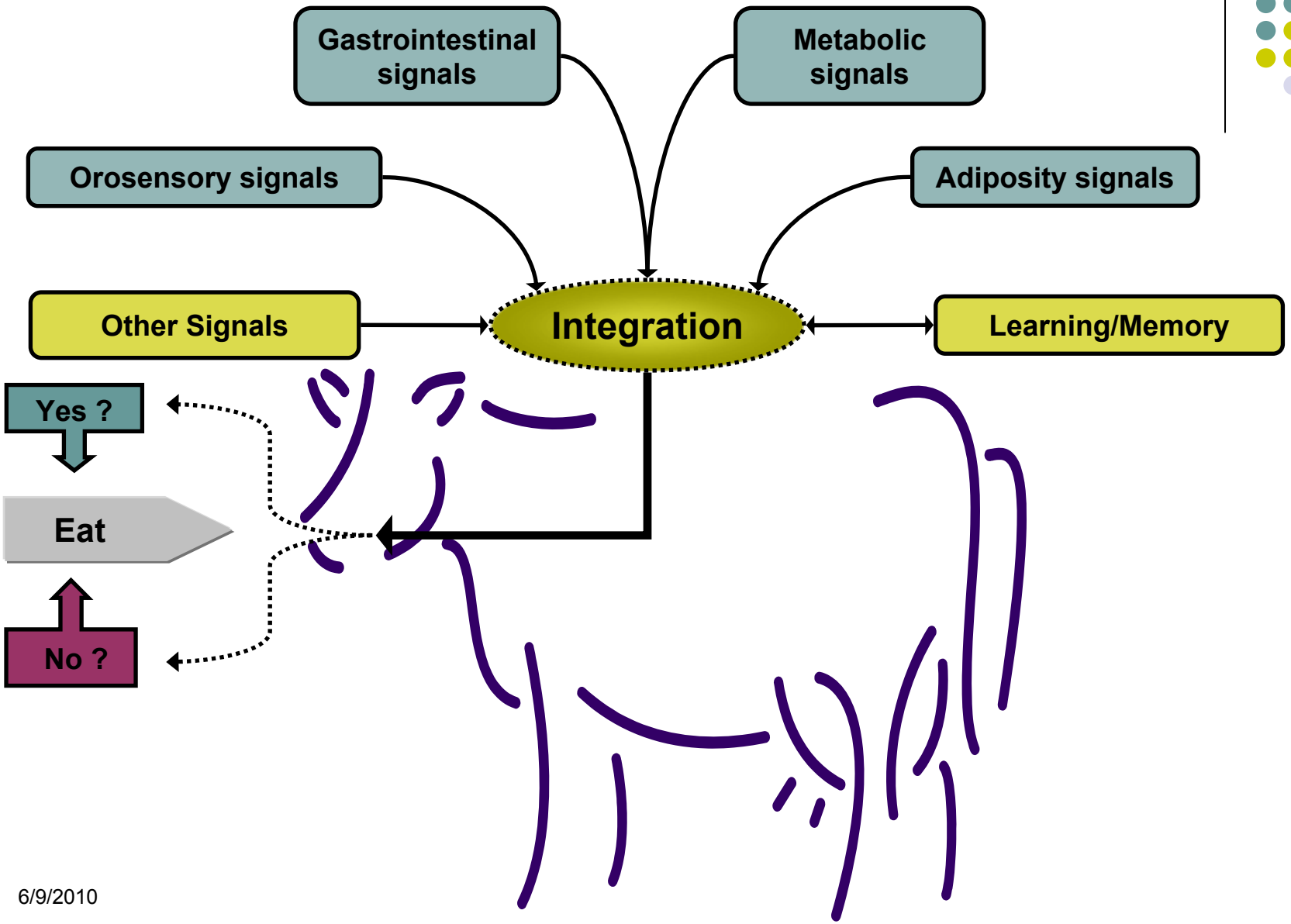
With ad libitum access to food, dairy cows eat about 10-14 discrete meals/24 hours



(Senn et al., Physiol. Behav. 58:229-236, 1995)

Control of meal size by stimulatory and inhibitory signals




Gastrointestinal signals
Metabolic signals
Orosensory signals
Adiposity signals
Other Signals
Integration
Learning/Memory
Yes ?
Eat
No ?

Verzehrsregulation

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Steuerung von Mahlzeitgrösse und -frequenz

- Orosensorische Signale
- Signale aus den Mägen
- Signale aus dem Dünndarm
- Metabolische Signale
- Pankreashormone

Angeborene Präferenzen und Aversionen

Positive Reaktion auf süss

Negative Reaktion auf bitter

(Berridge and Kringelbach, Psychopharmacology 2008)

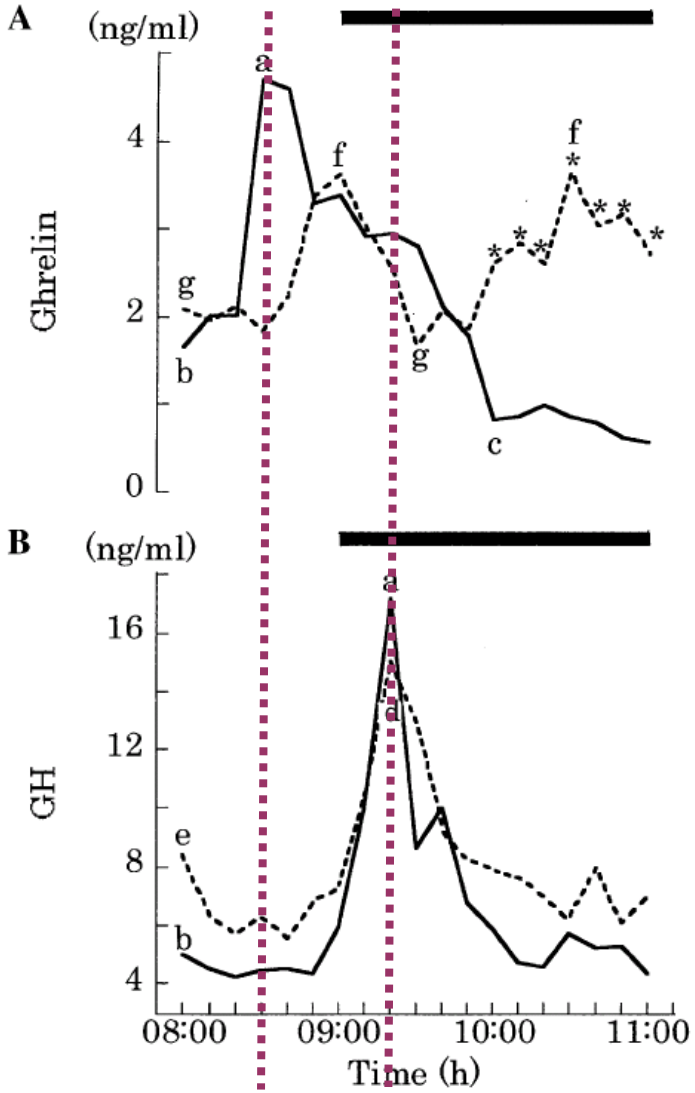
Lernprozesse bei der Nahrungswahl

Die sensorisch-spezifische Sättigung

Ghrelin

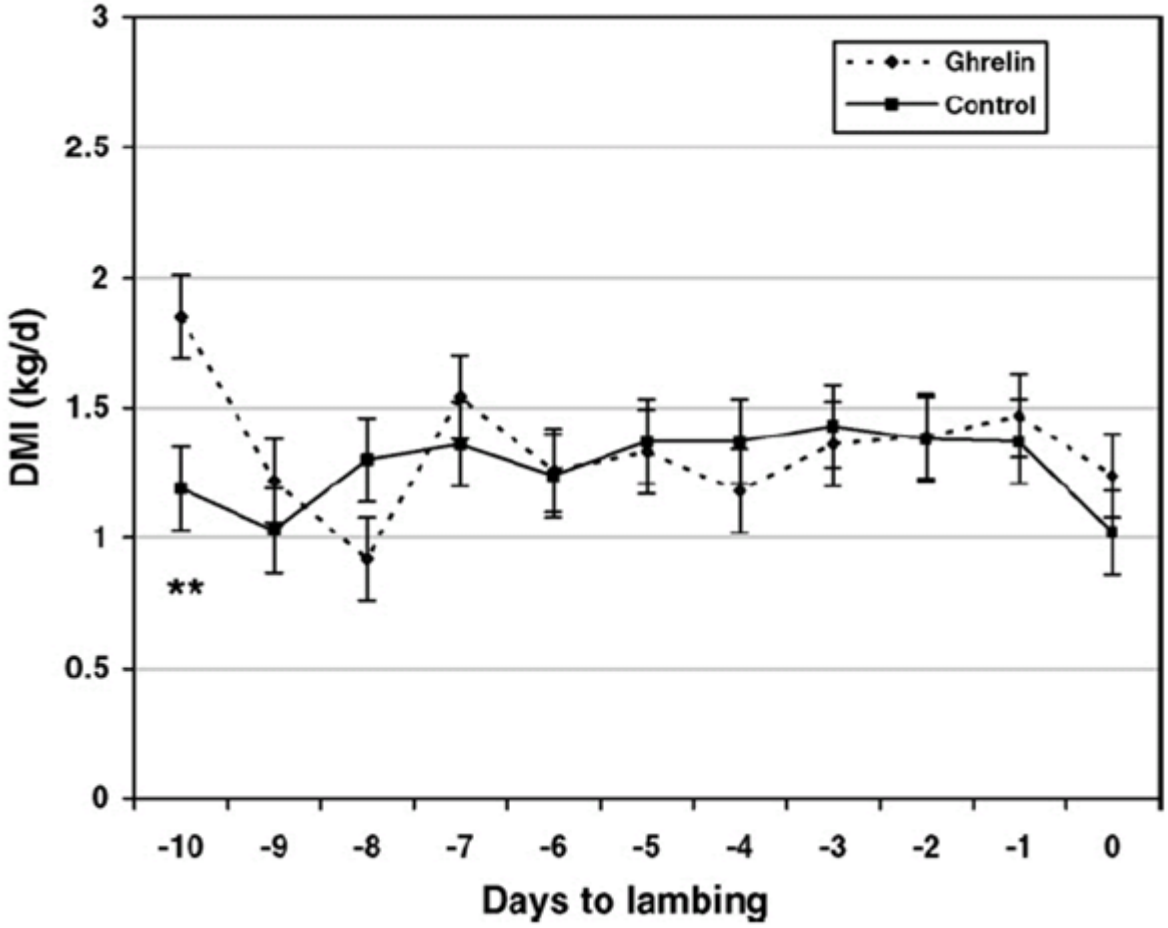
- gastric peptide with 28 amino acids
- stimulates GH release in vivo and in vitro
- circulating levels increased by starvation and reduced by refeeding
- stimulates food intake in animals and man, and chronic administration leads to overweight in rodents
- ICV antighrelin IgG inhibited eating in rodents
- circulating levels decreased in obesity in rodents and man
- NPY and AgRP are central mediators of the orexigenic effect

Plasma ghrelin and growth hormone concentration increase in relation to “real“ feeding (solid line) and “pseudo“ feeding (dotted line) in sheep



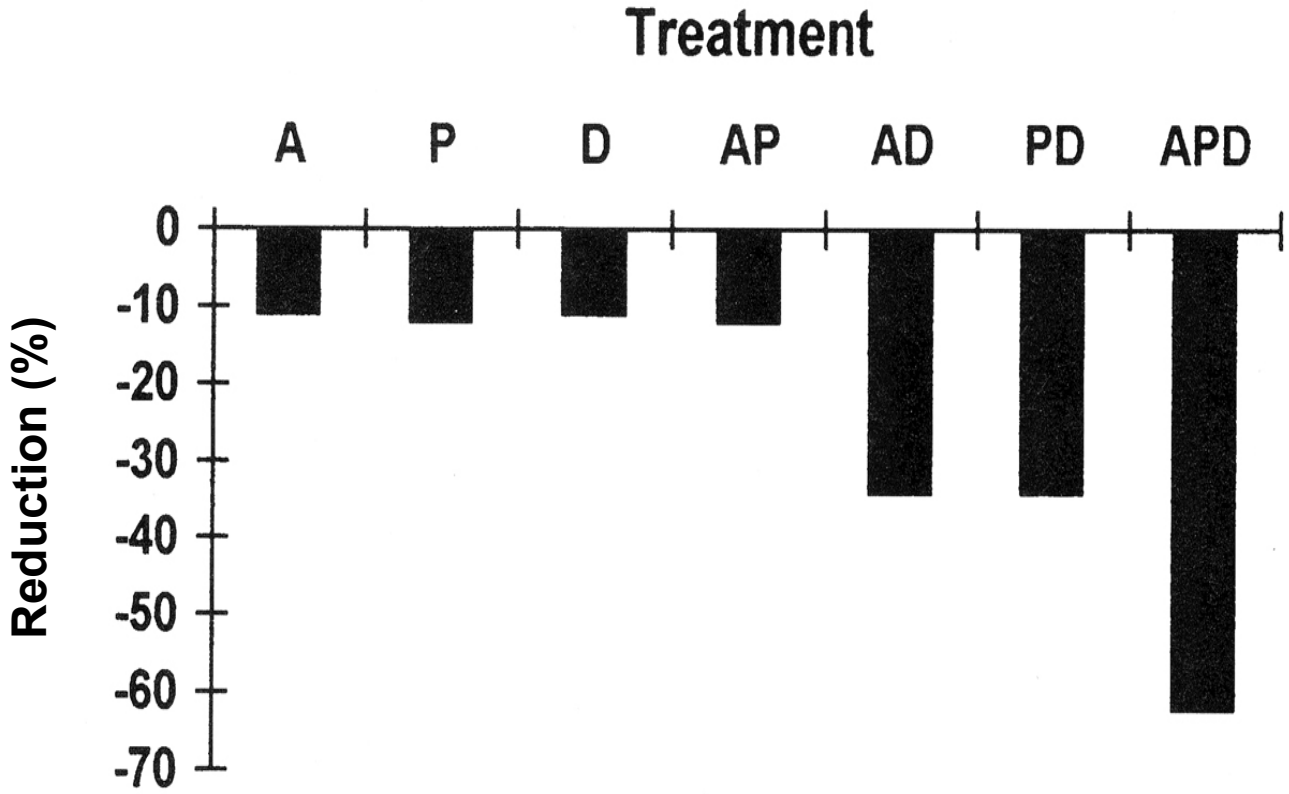
(Sugino et al., Biochem. Biophys. Res. Comm. 295: 255-260, 2002)

Short-term stimulatory effect of chronic IM ovine ghrelin on eating in sheep



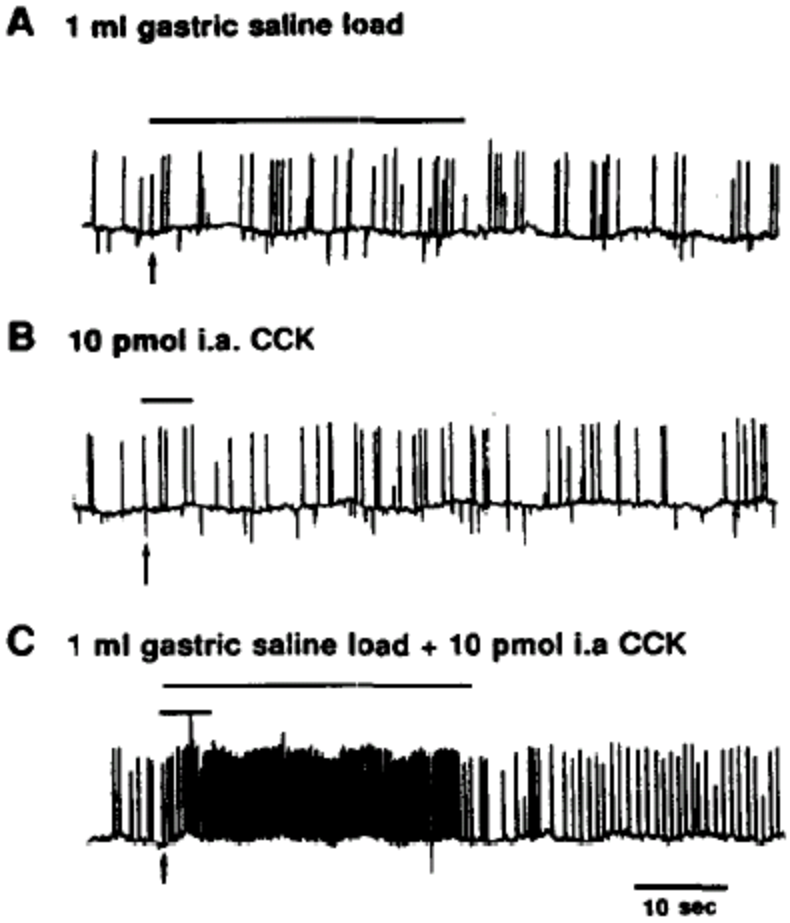
(Melendez et al. Theriogenology 66: 1961-1968, 2006)

Synergistic reduction of food intake in lactating cows caused by ruminal infusions of sodium acetate (A, 9mol/3h), propionate (P, 4mol/3h), and/or distension with a balloon (D, 10L/3h)

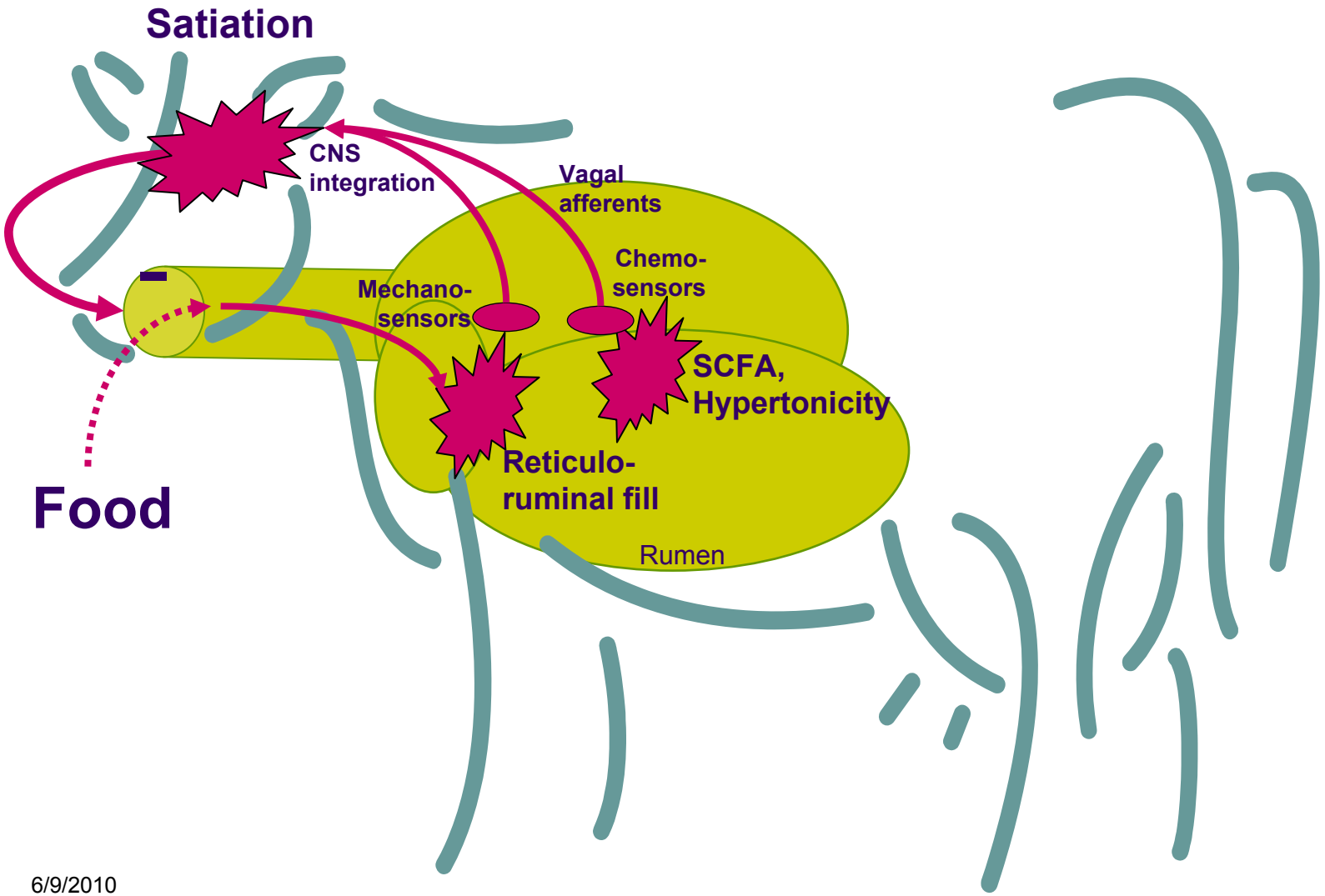


(Forbes, J. Anim. Sci. 74:3029-3035, 1996)

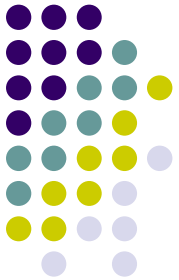
CCK and gastric load have a synergistic effect on gastric vagal afferent firing



(Schwartz and Moran, Neurosci. Biobehav. Rev. 20: 47-56, 1996)


Satiation
CNS integration
Vagal afferents
Chemo-sensors
Mechano-sensors
SCFA, Hypertonicity
Reticulo-ruminal fill
Food
Rumen

Gut peptides which inhibit eating in monogastric species:

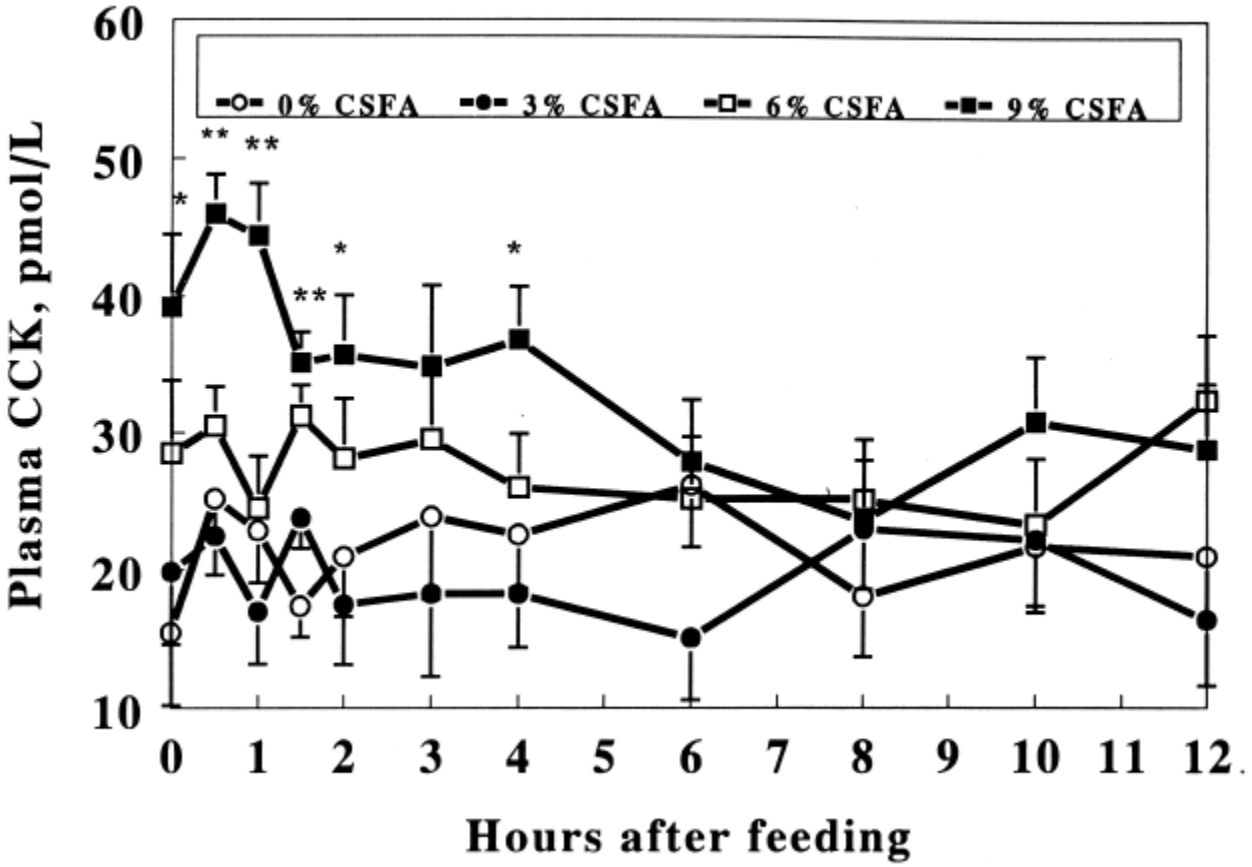


- Amylin
- Apolipoprotein A-IV
- Cholecystokinin (CCK)
- Enterostatin
- Gastrin-releasing-peptide
- Glucagon
- Glucagon-like peptide-1 (GLP-1)
- Glucagon-like peptide-2 (GLP-2)
- Insulin
- Neuromedin B
- Neurotensin
- Peptide YY(3-36)
- …

Physiological actions of CCK:

- Stimulation of gallbladder contraction
- Stimulation of pancreatic enzyme secretion
- Stimulation of pancreatic endocrine secretion
- Stimulation of pancreatic growth
- Regulation of digestive enzyme gene expression
  Inhibition of gastric emptying
- Satiation

Postprandial increase in plasma CCK in steers fed supplemental fat



(Choi et al., Dom. Anim. Endocrinol. 19:159-175, 2000)

The CCK-1 receptor antagonist MK-329 increases food intake in heifers fed a high fat diet

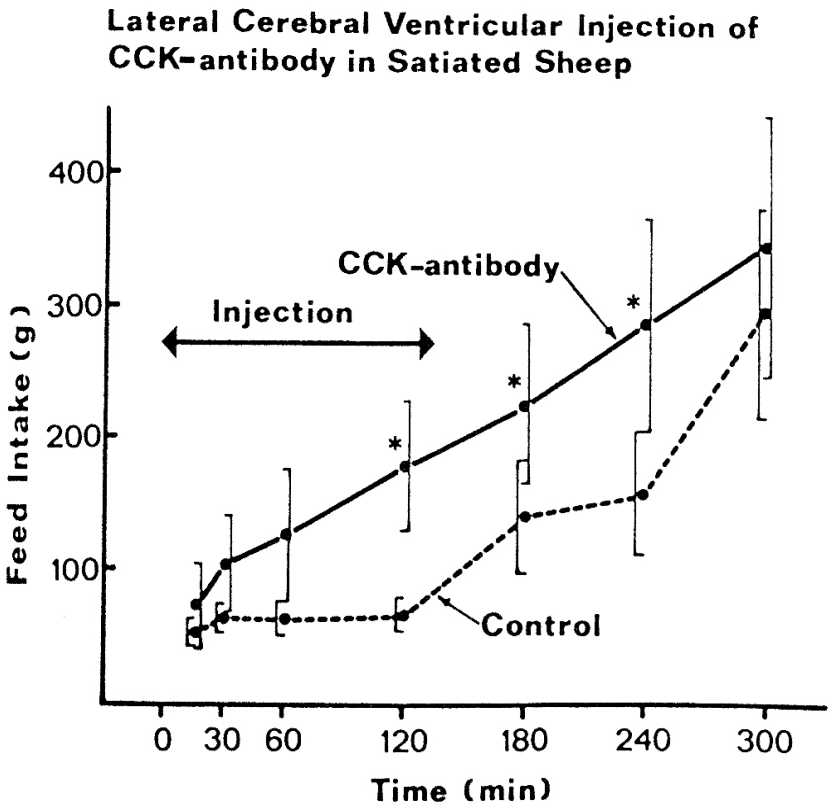
Table 3
Quantity of dry matter consumed per given time before and after intravenous injections of vehicle or MK-329 (70 μg/kg body weight) to dairy heifers fed low or high fat diets

	Treatments[a]				SEM	Effects, P <		
	LV	LM	HV	HM		Diet	MK[b]	Diet*MK
Postinjection, hr	----------(kg)----------							
−2[c]–0	2.28	2.30	1.99	1.93	0.24	NS	—	—
0–2	1.08	0.80	0.38	0.7	0.165	NS	NS	0.09
2–4	0.86	0.83	0.84	0.50	0.09	NS	NS	NS
−2–22	8.45	8.14	7.43	7.93	0.61	0.04	NS	NS

[a] Treatments; LV = low fat + vehicle, LM = low fat + MK-329, HV = high fat + vehicle, and HM = high fat + MK-329 (n = 4 for each treatment).
[b] MK-329 or vehicle.
[c] Feeding was at −2 hr.

(Choi et al., Dom. Anim. Endocrinol. 19:159-175, 2000)

ICV CCK AB increases food intake in sheep

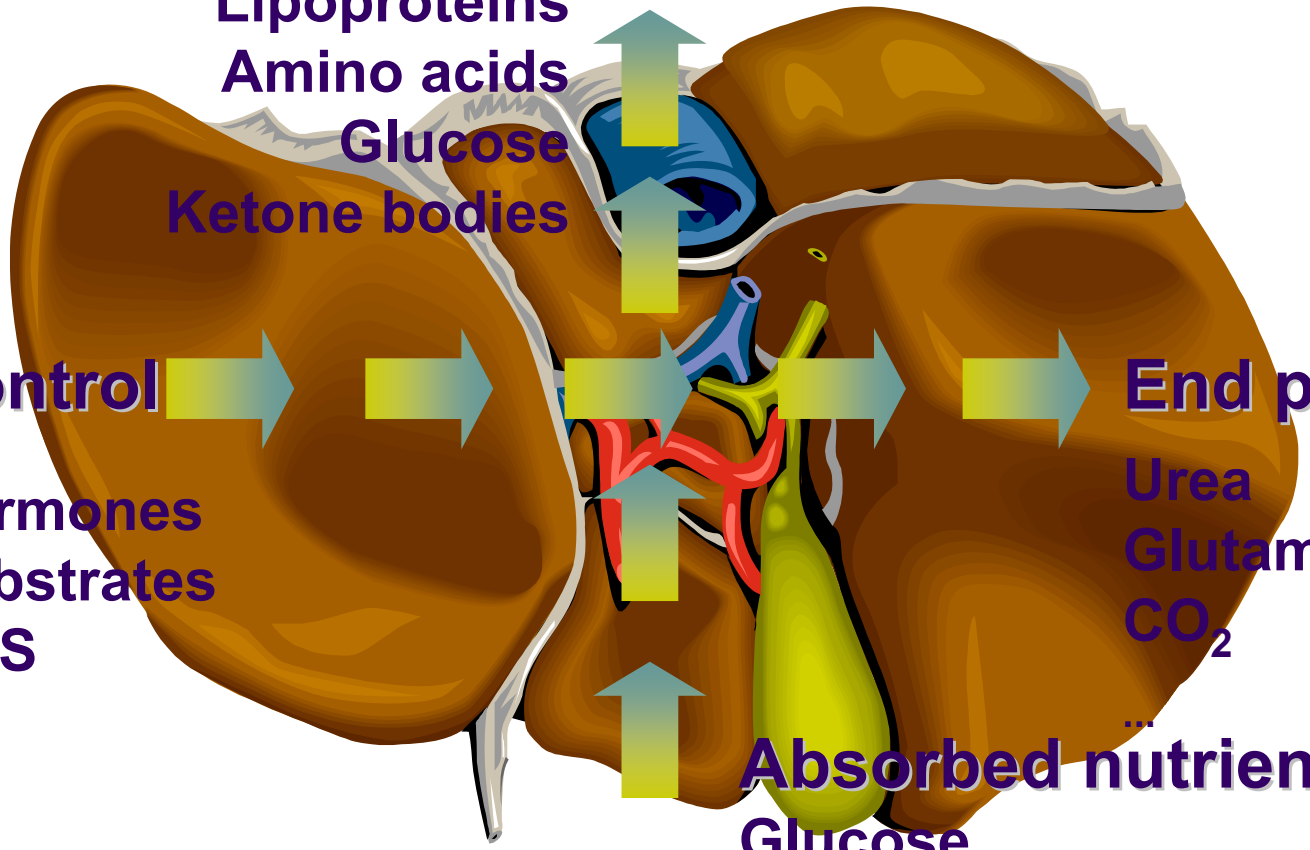


(Della-Fera et al., Science 212:687-689, 1981)

→ Argues for a physiological satiety effect of CCK in ruminants !

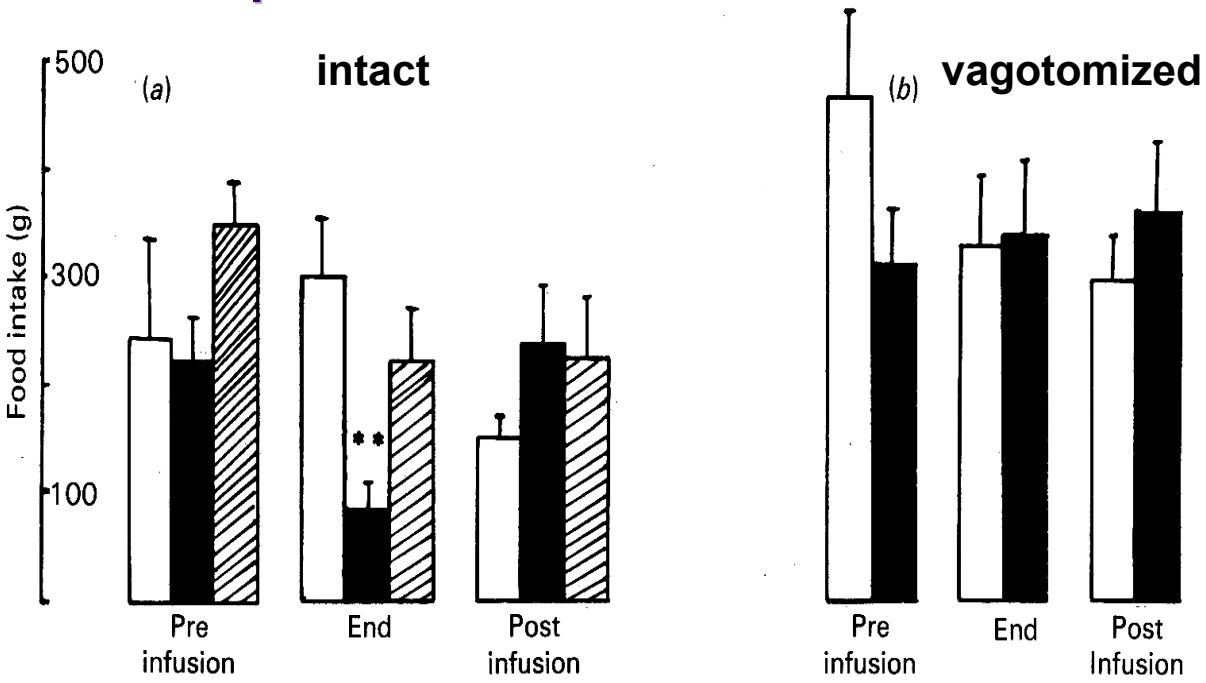
Two possible "mechanistic" explanations:

1) **Circulating endogenous CCK acts centrally to inhibit eating**
2) **CNS endogenous CCK is involved in satiation**



G. Lobley, presented at ISRP, Pretoria, October 1999 (with modifications)

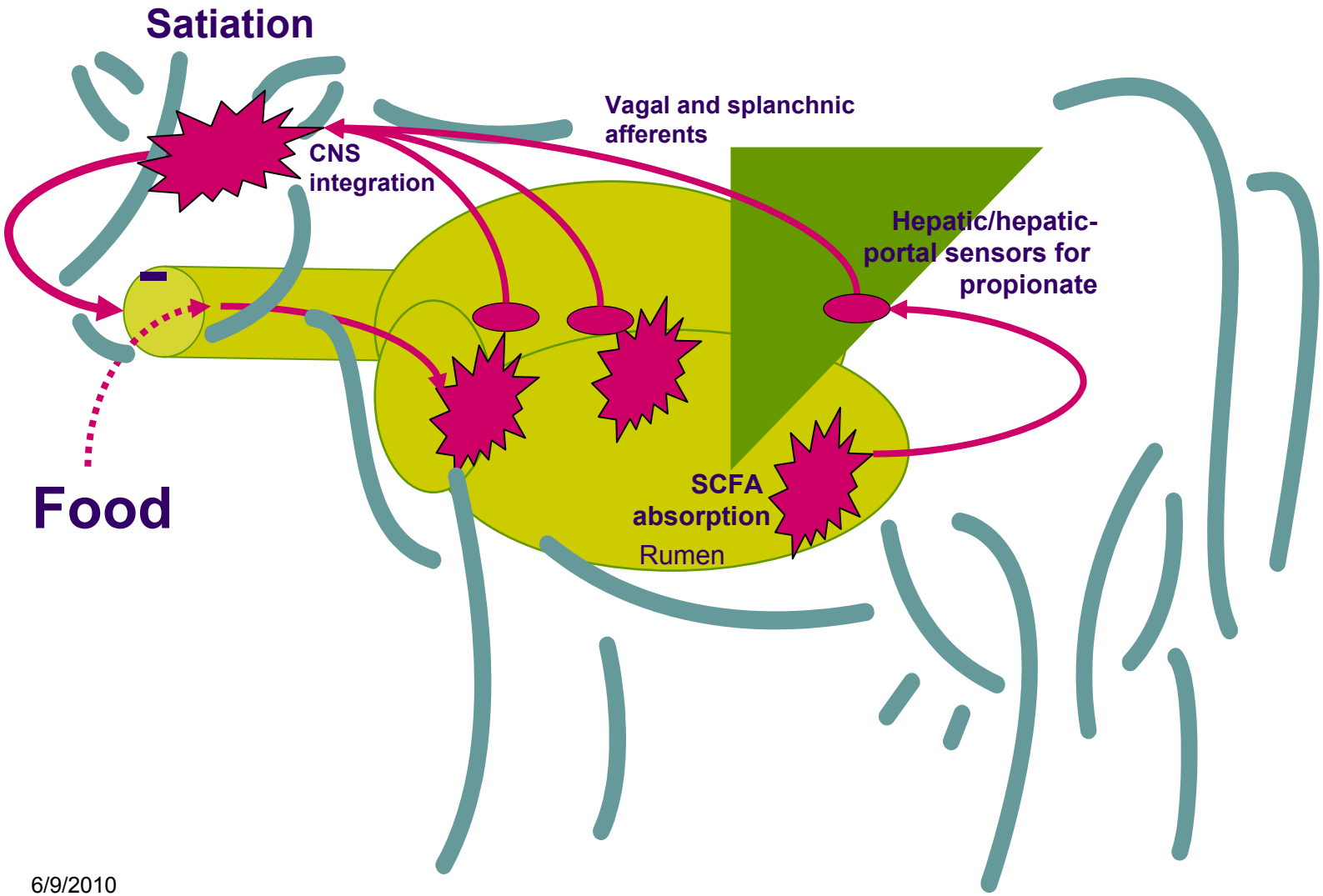
Vagotomy and splanchnic nerve blockade with anesthetic block the hypophagic effect of intraportal propionate infusion in sheep



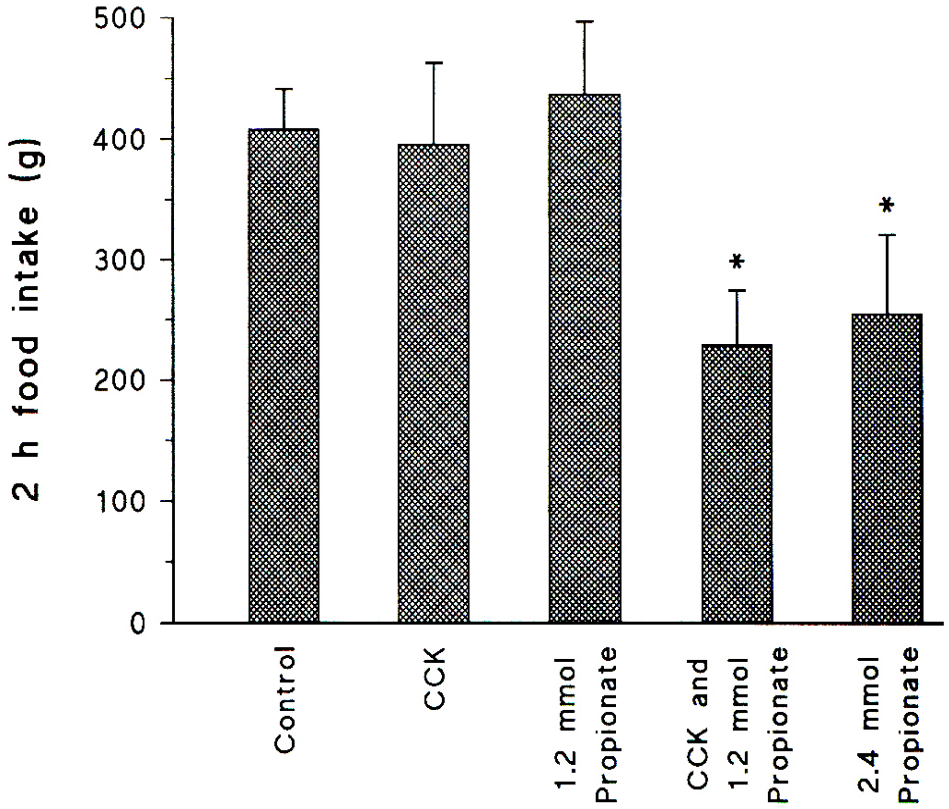
Saline Na-propionate (1.2 mmol/min x 3h)

Splanchnic nerve blocked with anesthetic and propionate infused

(Anil & Forbes, Proc. Nutr. Soc. 46:125-133, 1987)


Satiation
CNS integration
Vagal and splanchnic afferents
Hepatic/hepatic-portal sensors for propionate
Food
SCFA absorption
Rumen

Synergistic reduction of food intake by IV propionate and CCK in sheep



(Farningham et al., Physiol. Behav. 54:437-442, 1993)

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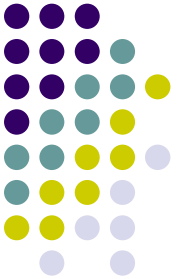
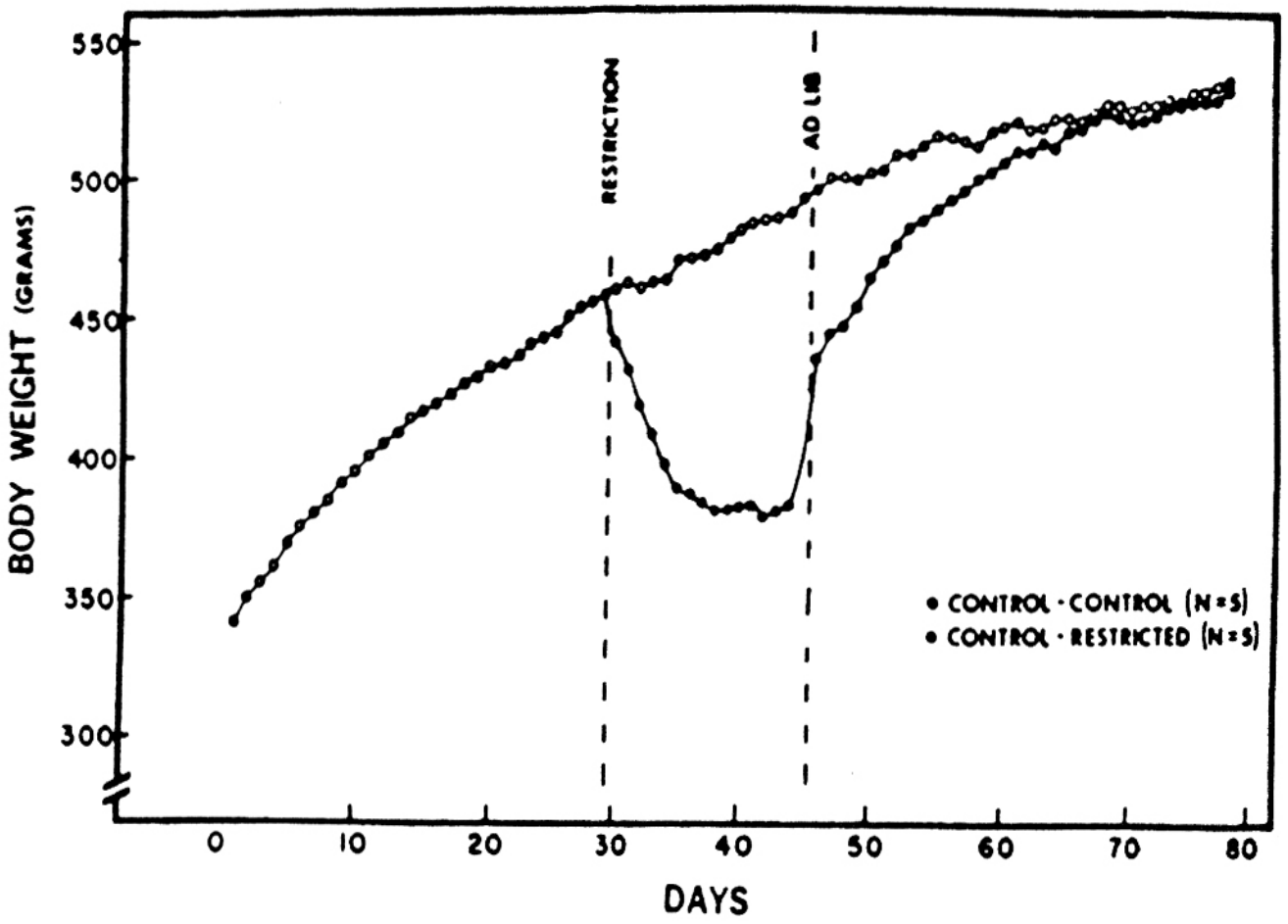
Evidence for a physiological control of body (fat) mass:



- The body weight of adult individuals remains surprisingly constant over long periods of time
- If body weight in adult individuals (and thus body fat) is forced away from its normal level, compensatory changes in food intake and energy expenditure are induced
- Several lines of evidence suggest that this compensation is more effective when body weight is decreased (instead of increased)

Recovery of rats‘ body weight after a period of caloric restriction



(Keesey and Hirvonen, J. Nutr. 127:1875S-1883S, 1997)

When leptin entered the picture…

Positional cloning of the mouse *obese* gene and its human homologue

Yiying Zhang*†, Ricardo Proenca*†, Margherita Maffei†, Marisa Barone*†, Lori Leopold*† & Jeffrey M. Friedman*†‡

* Howard Hughes Medical Institute, † The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

The mechanisms that balance food intake and energy expenditure determine who will be obese and who will be lean. One of the molecules that regulates energy balance in the mouse is the *obese* (*ob*) gene. Mutation of *ob* results in profound obesity and type II diabetes as part of a syndrome that resembles morbid obesity in humans. The *ob* gene product may function as part of a signalling pathway from adipose tissue that acts to regulate the size of the body fat depot.

OBESITY is the commonest nutritional disorder in Western societies. More than three in ten adult Americans weigh at least 20% in excess of their ideal body weight[1]. Increased body weight is an important public health problem because it is associated with type II diabetes, hypertension, hyperlipidaemia and certain cancers[2]. Although obesity is often considered to be a psychological problem, there is evidence that body weight is physiologically regulated[3].

The molecular pathogenesis of obesity is unknown. To identify components of the physiological system controlling body weight, we have applied positional cloning technologies in an attempt to isolate mouse obesity genes. Five single-gene mutations in mice that result in an obese phenotype have been described[3]. The first of the recessive obesity mutations, the *obese* mutation (*ob*), was identified in 1950[4]. *ob* is a single gene mutation that results in profound obesity and type II diabetes as part of a syndrome that resembles morbid obesity in humans[5]. Neither the primary defect nor the site of synthesis of the *ob* gene product is known. Cross-circulation experiments between mutant and wild-type mice suggest that *ob* mice are deficient for a blood-borne factor that regulates nutrient intake and metabolism[6], but the nature of this putative factor has not been determined.

We report the cloning and sequencing of the mouse *ob* gene and its human homologue. *ob* encodes a 4.5-kilobase (kb) adipose tissue messenger RNA with a highly conserved 167-amino-acid open reading frame. The predicted amino-acid sequence is 84% identical between human and mouse and has features of a secreted protein. A nonsense mutation in codon 105 has been found in the original congenic C57BL/6J *ob*/*ob* mouse strain, which expresses a twentyfold increase in *ob* mRNA. A second *ob* mutant, the co-isogenic SM/Ckc-$+^{Dac}ob^{3J}/ob^{3J}$ strain, does not synthesize *ob* RNA. These data suggest that the *ob* gene product may function as part of a signalling pathway from adipose tissue that acts to regulate the size of the body fat depot.

For the positional cloning of mutant genes from mammals, it is necessary first to obtain genetic and physical maps, then to isolate the gene and detect the mutation. Here we describe the successful use of this approach to identify the *ob* gene.

Genetic and physical mapping of *ob*

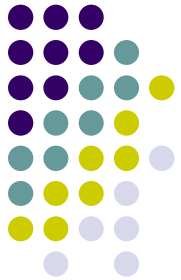
The first *ob* mutation (carried on the congenic C57Bl/6J *ob*/*ob* strain) was found proximal to the *Microphthalmia* (*Mi*) and *waved-1* (*wav-1*) loci on proximal mouse chromosome 6 (ref. 7); a second co-isogenic allele of *ob* has been identified in the SM/Ckc-Dac mouse strain (S. Lane, personal communication).

We previously positioned *ob* relative to a series of molecular markers on mouse chromosome 6 and mapped the *ob* gene close to a restriction-fragment length polymorphism (RFLP) marker, D6Rck 13, derived from chromosome microdissection[5,8]; we also found that *Pax4* in the proximal region of mouse chromosome 6 is tightly linked to *ob* (ref. 9). Both loci were initially used to type a total of 835 informative meioses derived from both interspecific and intersubspecific mouse crosses that were segregating *ob*. *Pax4* was mapped proximal to *ob* and was recombinant in two animals (111 and 420 in Fig. 1); no recombination between D6Rck13 and *ob* was detected among the first 835 meioses scored[9].

To isolate the *ob* gene we cloned the DNA in the region of *Pax4* and D6Rck13 (Fig. 1), using both probes to start the construction of a physical map in the region of *ob*. Yeast artificial chromosomes (YACs) corresponding to *Pax4* and D6Rck13 were isolated and characterized. Centromeric and telomeric ends of each YAC were recovered, and ends mapping closer to *ob* used to screen for new YACs. YAC ends were recovered using either vectorette polymerase chain reaction (PCR) or the plasmid end-rescue technique[10,11]. One of the ends (labelled (1) in Fig. 1) of a D6Rck13 YAC, 902A0653, was recombinant in animal 257, positioning *ob* between this YAC end and *Pax4*. We were unable to recover any YACs linking the ends of YACs yB1S4A5 and 902A0653 (labelled (2) and (3) in Fig. 1). Pulsed-field gel electrophoresis (PFGE) indicated that there was a ~70-kb gap separating the two YAC ends. To bridge this gap, we used both YAC ends to isolate a set of mouse P1 clones[12,13]. Analysis of the ends of these P1 clones showed that they overlapped and that the gap in the YAC contig was ~70 kb. The size of the contig spanning the *ob* locus was 2.2 megabases (Mb) and *ob* was localized to the 900 kb between the distal end of YAC 903E1016 (labelled (5) in Fig. 1) and the distal end of YAC 902A0653 (labelled (1) in Fig. 1).

To position *ob* more precisely, we genotyped an additional 771 meioses derived from both a C57BL/6J *ob*/*ob* × DBA/2J intercross and backcross[5]. The typing of the intraspecific crosses required the development of informative single-strand length polymorphisms (SSLPs) for both D6Rck13 and Pax4. Sequencing of the *Pax4* gene itself revealed a microsatellite sequence, and an SSLP near D6Rck13, D6Rck39, was identified by sequencing cosmid subclones from YAC y902A0653 (a YAC isolated with D6Rck13). PCR amplification of genomic DNA with primers flanking these microsatellites revealed polymorphisms among the various progenitor strains of the genetic crosses. No additional recombinants between *ob* and *Pax4* were identified after genotyping the obese backcross and intercross progeny from the crosses to DBA mice. The genetic results indicated that D6Rck39 was distal to *ob* and recombined with *ob* in a single obese animal

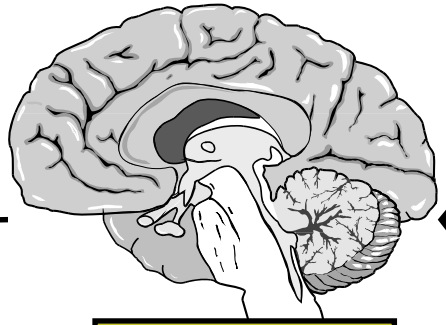
‡ To whom correspondence should be addressed.



Criteria for an adiposity signal:

- directly proportional to fat mass
- circulating in the blood
- access to the brain
- predictable effects on food intake and metabolism

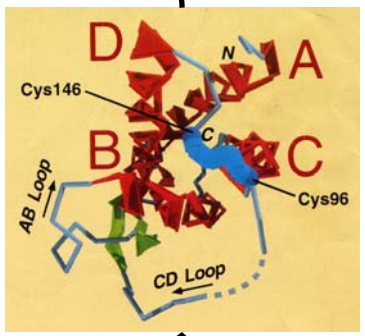
Receptors in:
- Hypothalamus (arcuate, lateral, ventromedial and dorsomedial nuclei)
- Hindbrain (AP, NTS, DMX)
- Choroid plexus



Saturable transport into brain

Leptin

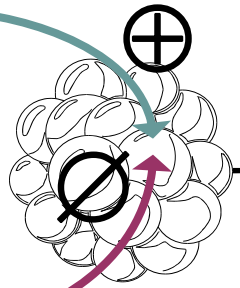
- molecular weight: 16‘000
- in plasma bound to protein(s)
- positively correlated with BMI
- half life about 25min



Metabolism

Food intake

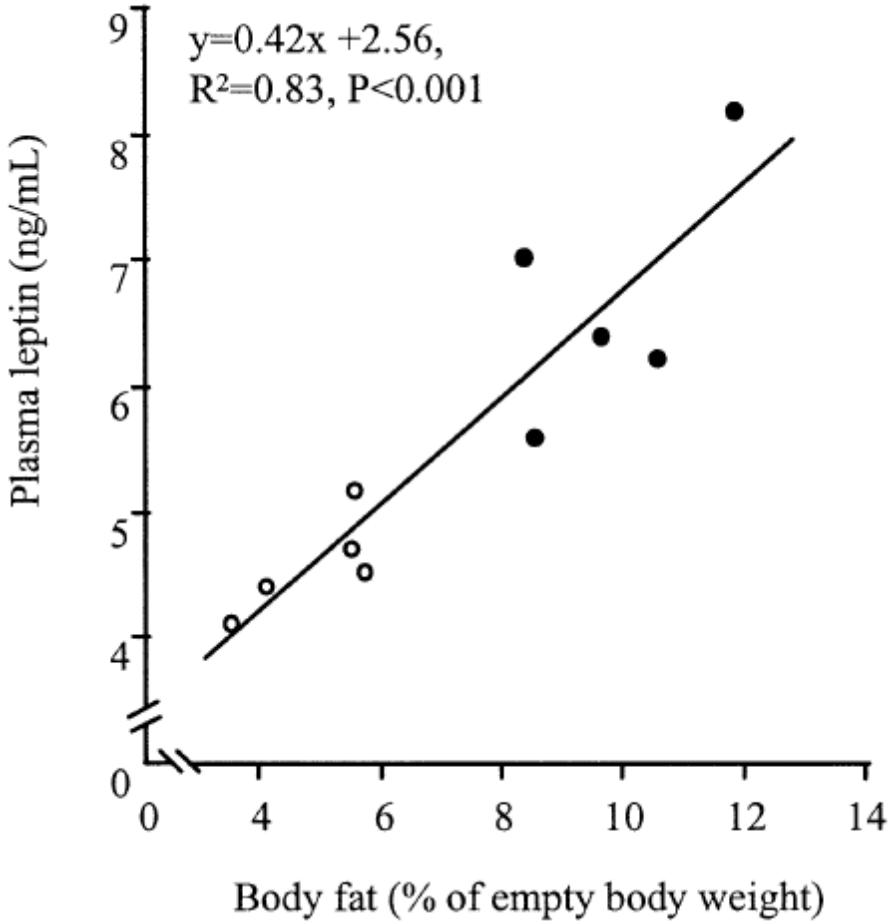
- Insulin
- Glucocorticoids
- Eating
- Weight gain
- 17β estradiol
- Cytokines



- Weight loss
- β3-agonists
- Fasting

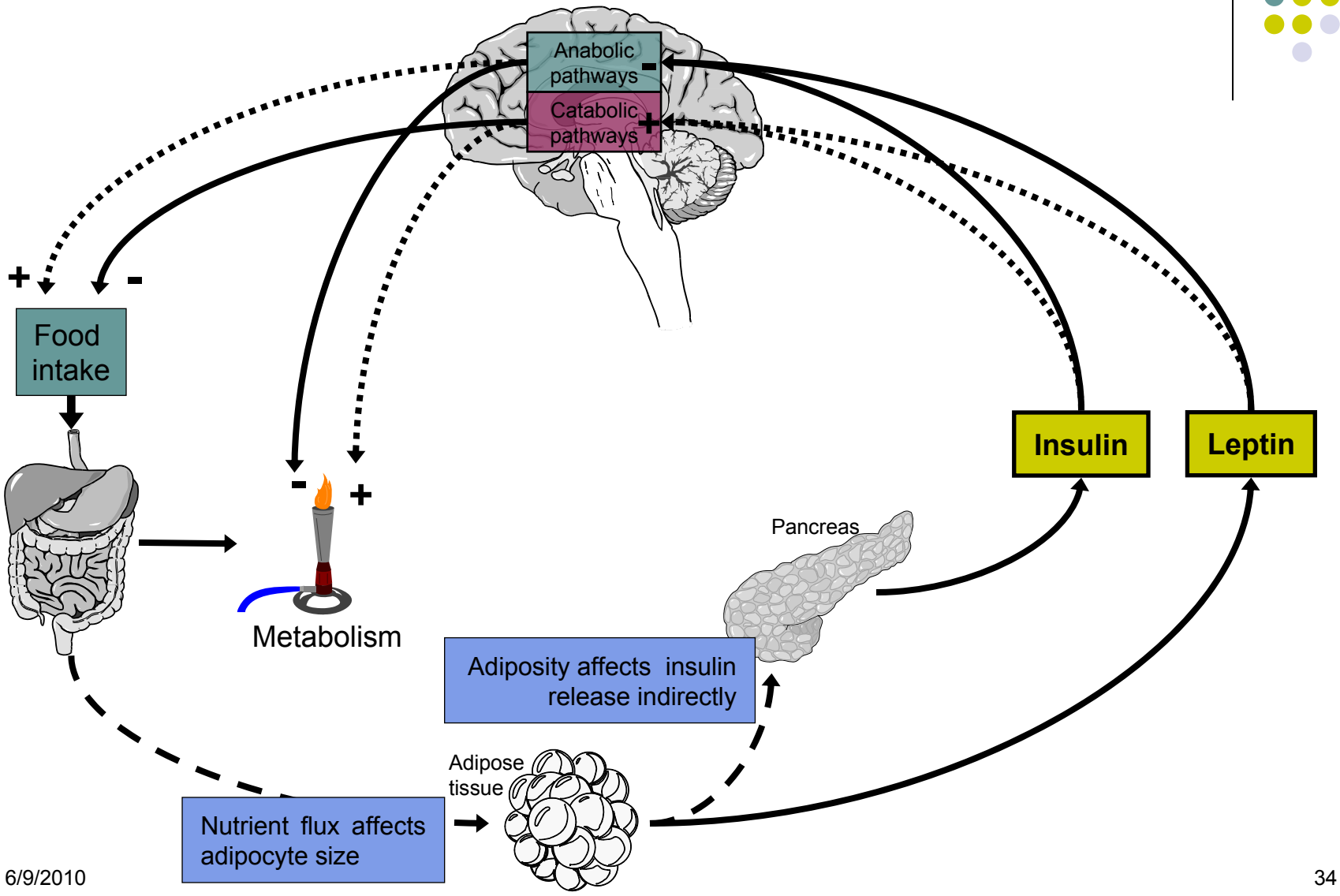
Production in adipose tissue (subcutaneous > mesenteric) in relation to adipocyte size

Plasma leptin concentration is directly related to body fat in ruminants

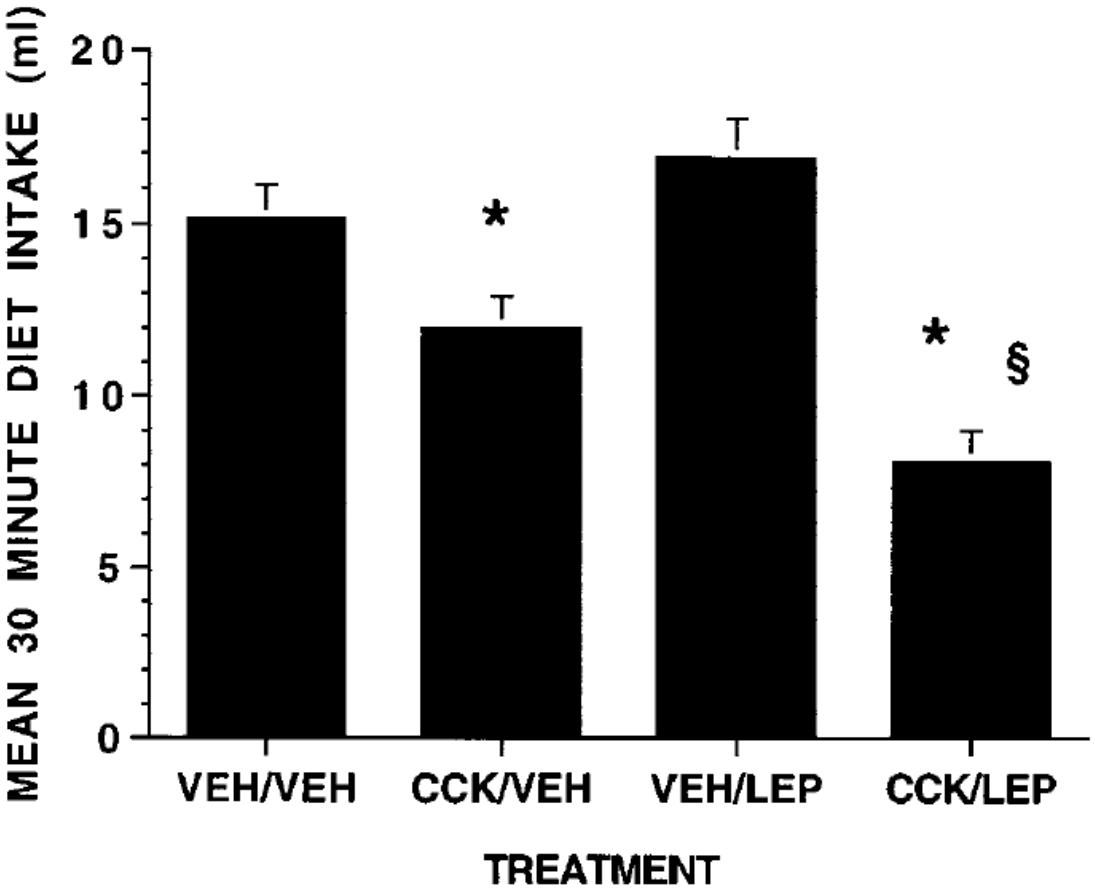


(Ingvartsen et al., Dom. Anim. Endocrinol. 21:215-250, 2001)

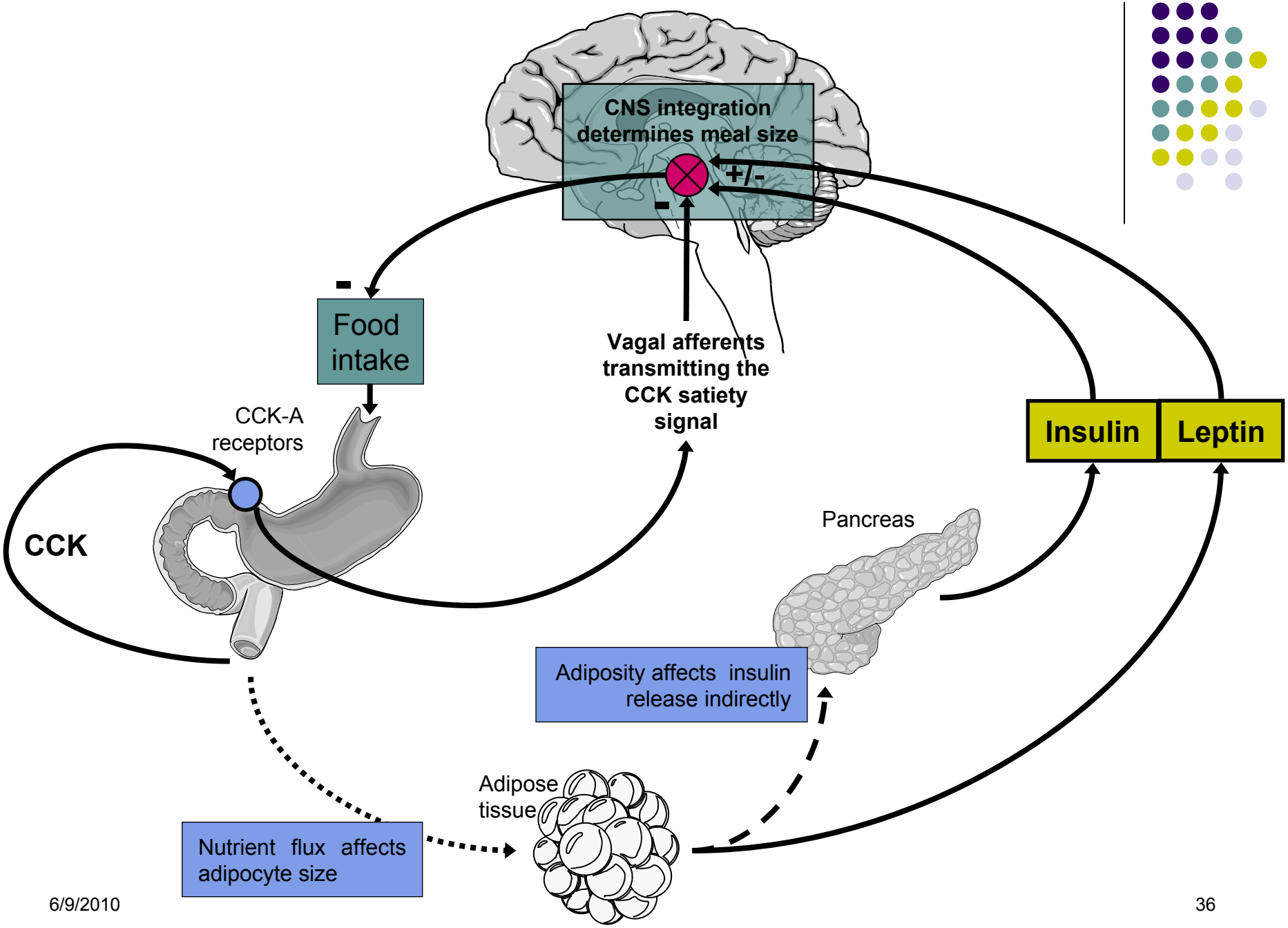
Adiposity signals



Leptin (10μg ICV) enhances the eating-inhibitory effect of CCK (1nmol/kg IP)



(Emond et al., Am. J. Physiol. 276:R1545-R1549, 1999)


CNS integration determines meal size
+/-
-
-
Food intake
Vagal afferents transmitting the CCK satiety signal
CCK-A receptors
CCK
Insulin
Leptin
Pancreas
Adiposity affects insulin release indirectly
Adipose tissue
Nutrient flux affects adipocyte size

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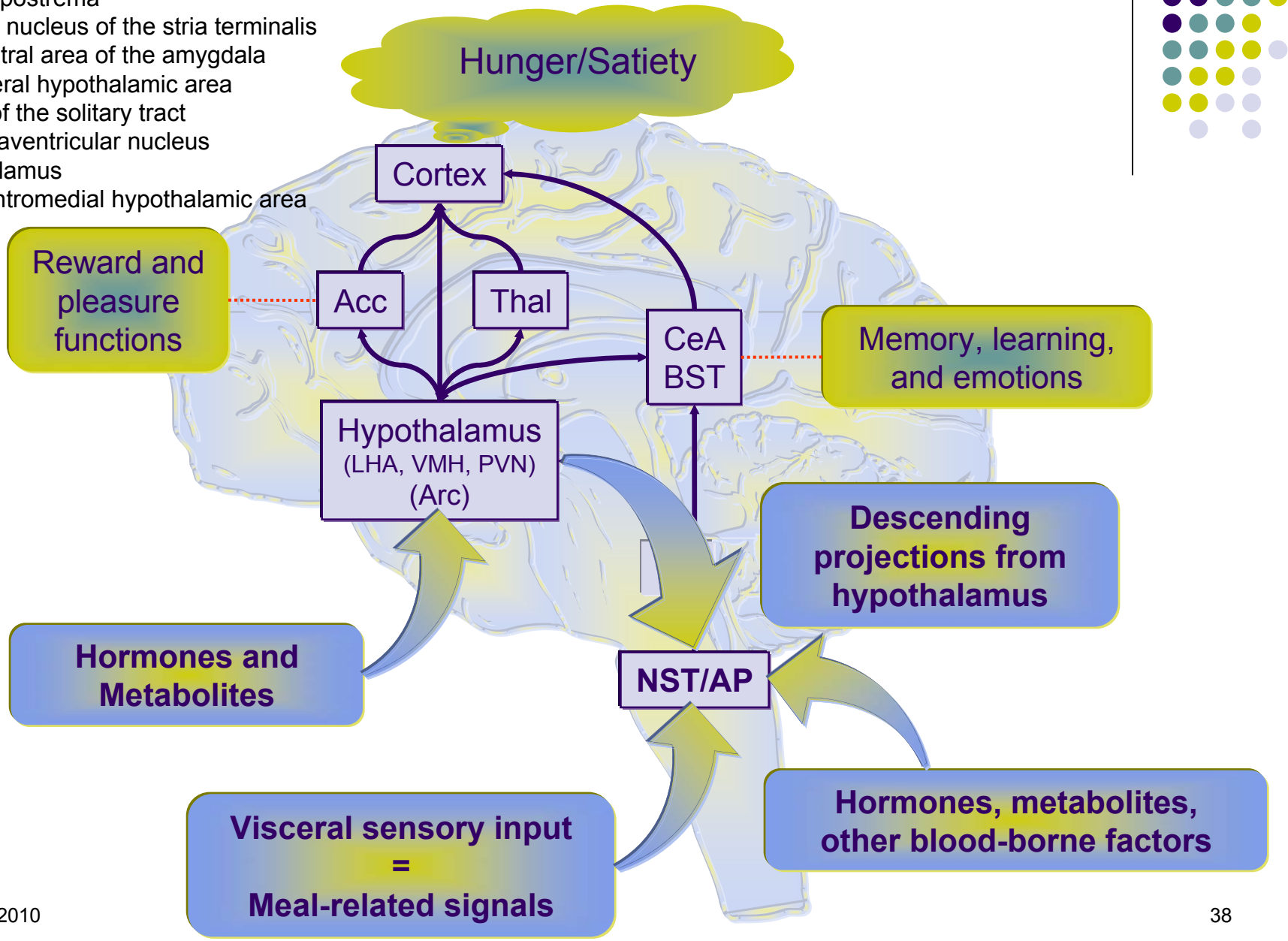
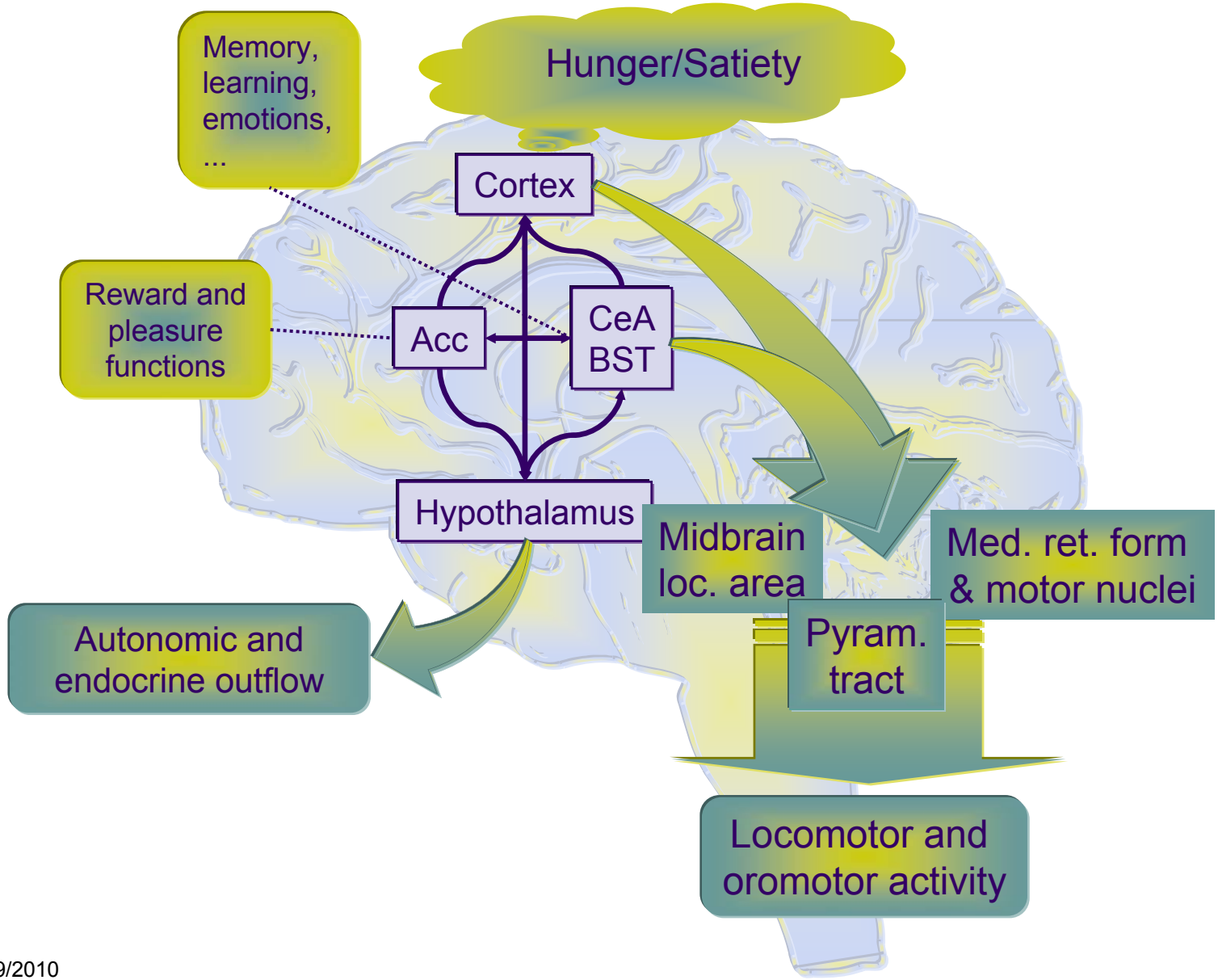
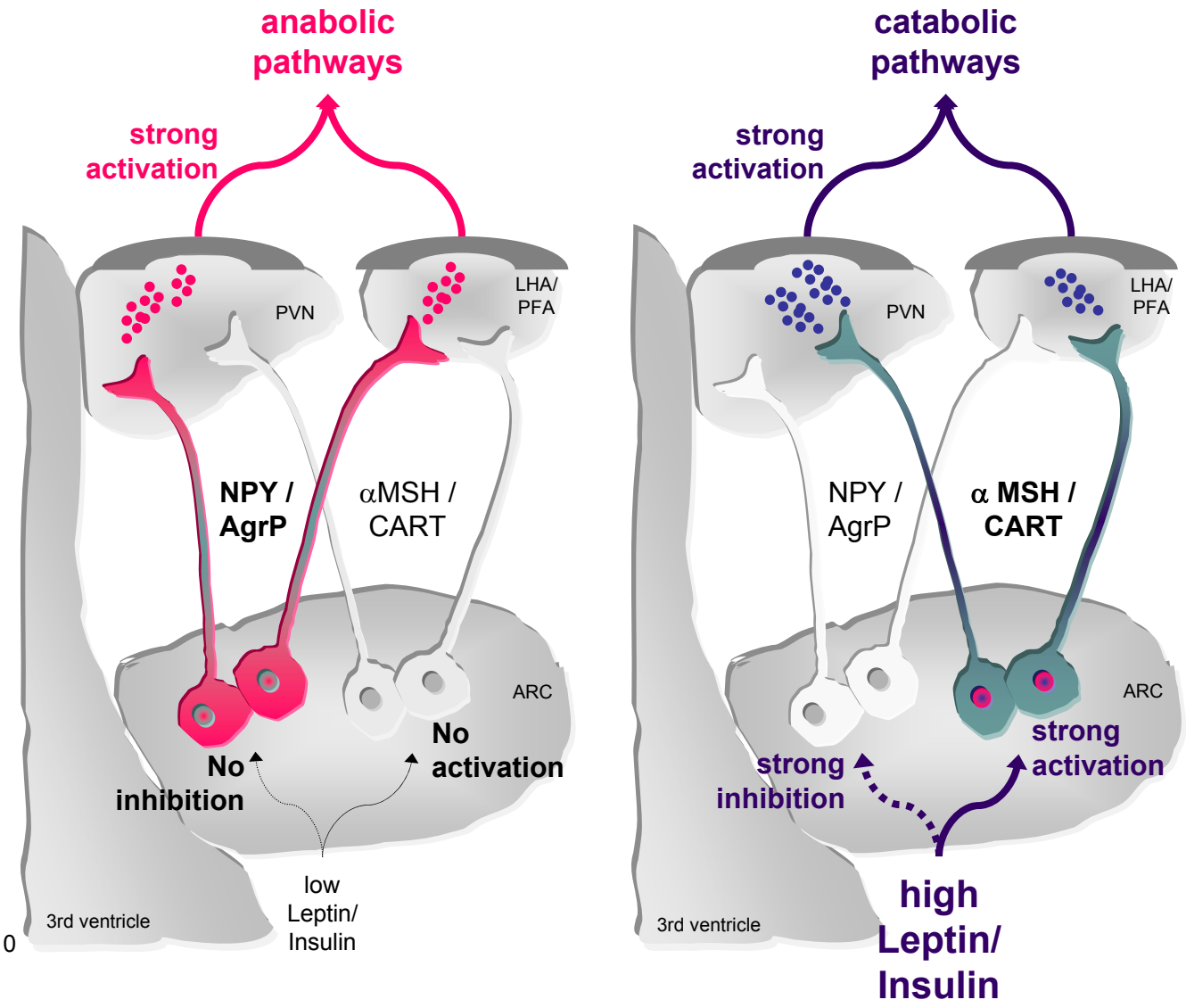
Acc: N. accumbens
Arc: Arcuate nucleus
AP: Area postrema
BST: Bed nucleus of the stria terminalis
CeA: Central area of the amygdala
LHA: Lateral hypothalamic area
NST: N. of the solitary tract
PVN: Paraventricular nucleus
Thal: Thalamus
VMH: Ventromedial hypothalamic area



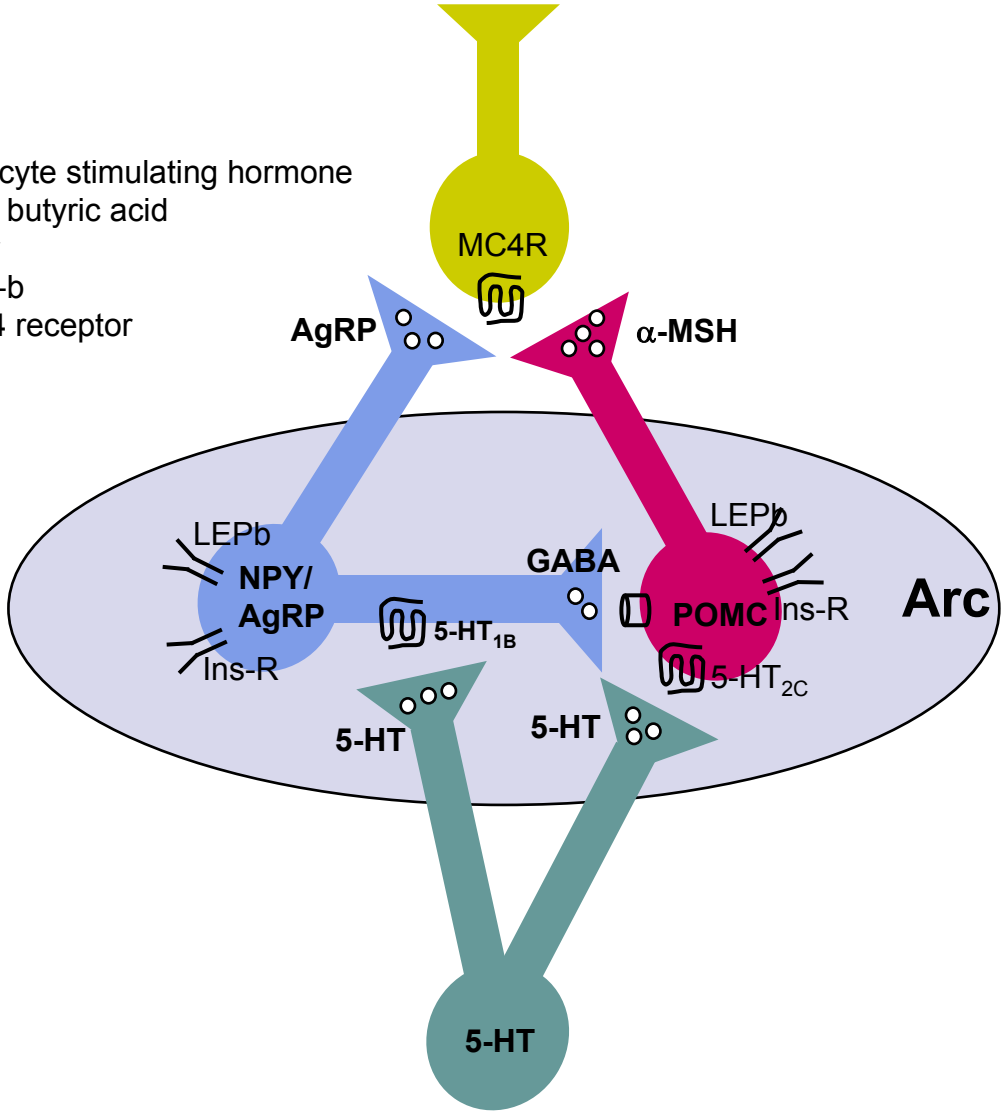

Memory, learning, emotions, ...
Hunger/Satiety
Cortex
Reward and pleasure functions
Acc
CeA BST
Hypothalamus
Midbrain loc. area
Med. ret. form & motor nuclei
Pyram. tract
Autonomic and endocrine outflow
Locomotor and oromotor activity

Anabolic and catabolic neuropeptide pathways in the hypothalamus and their modulation by leptin and insulin

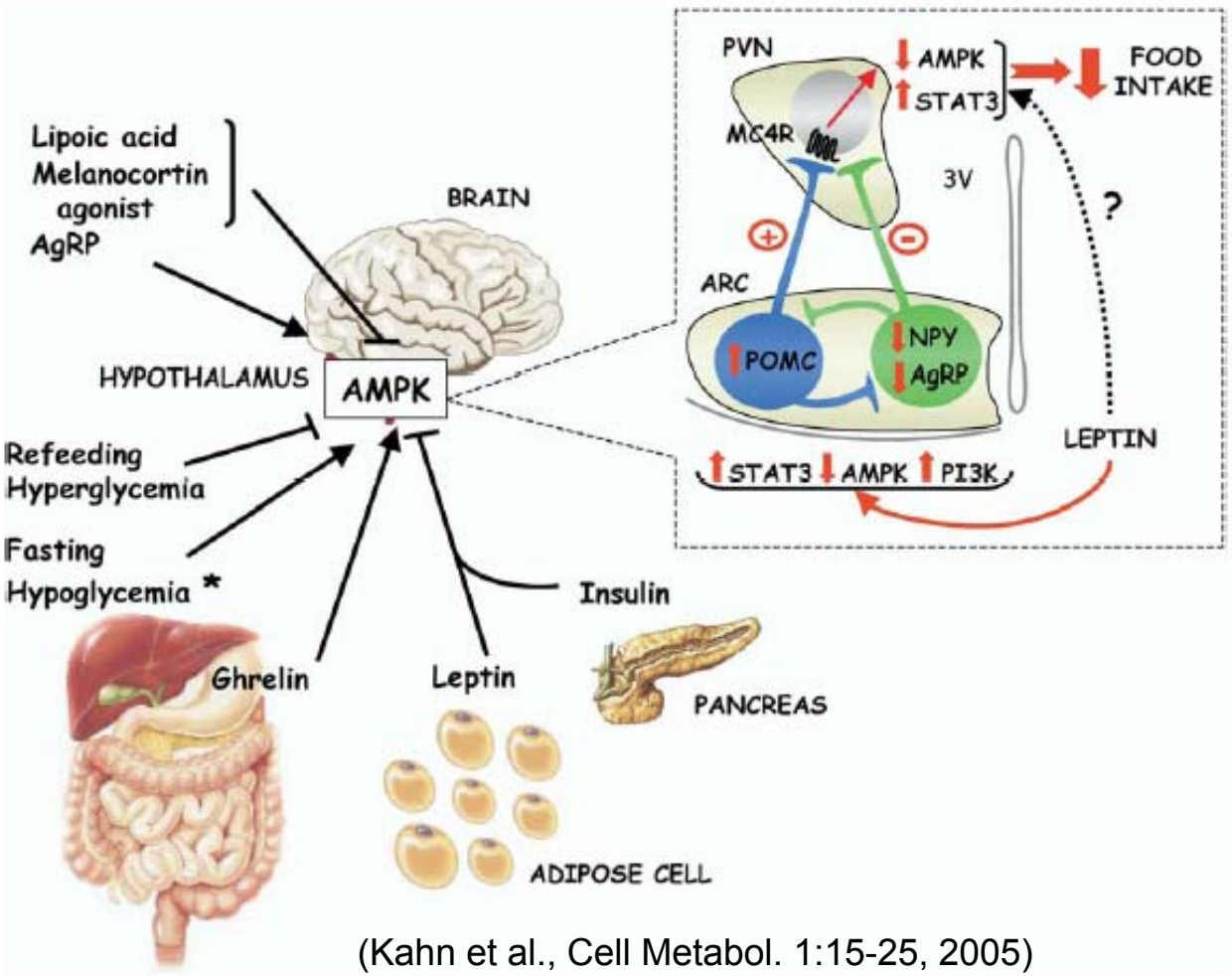


Current concept of connectivity of NPY/AgRP and POMC neurons in the hypothalamus

5-HT: Serotonin
α-MSH: alpha-melanocyte stimulating hormone
GABA: gamma-amino butyric acid
Ins-R: Insulin receptor
LEPb: Leptin receptor-b
MC4R: Melanocortin-4 receptor

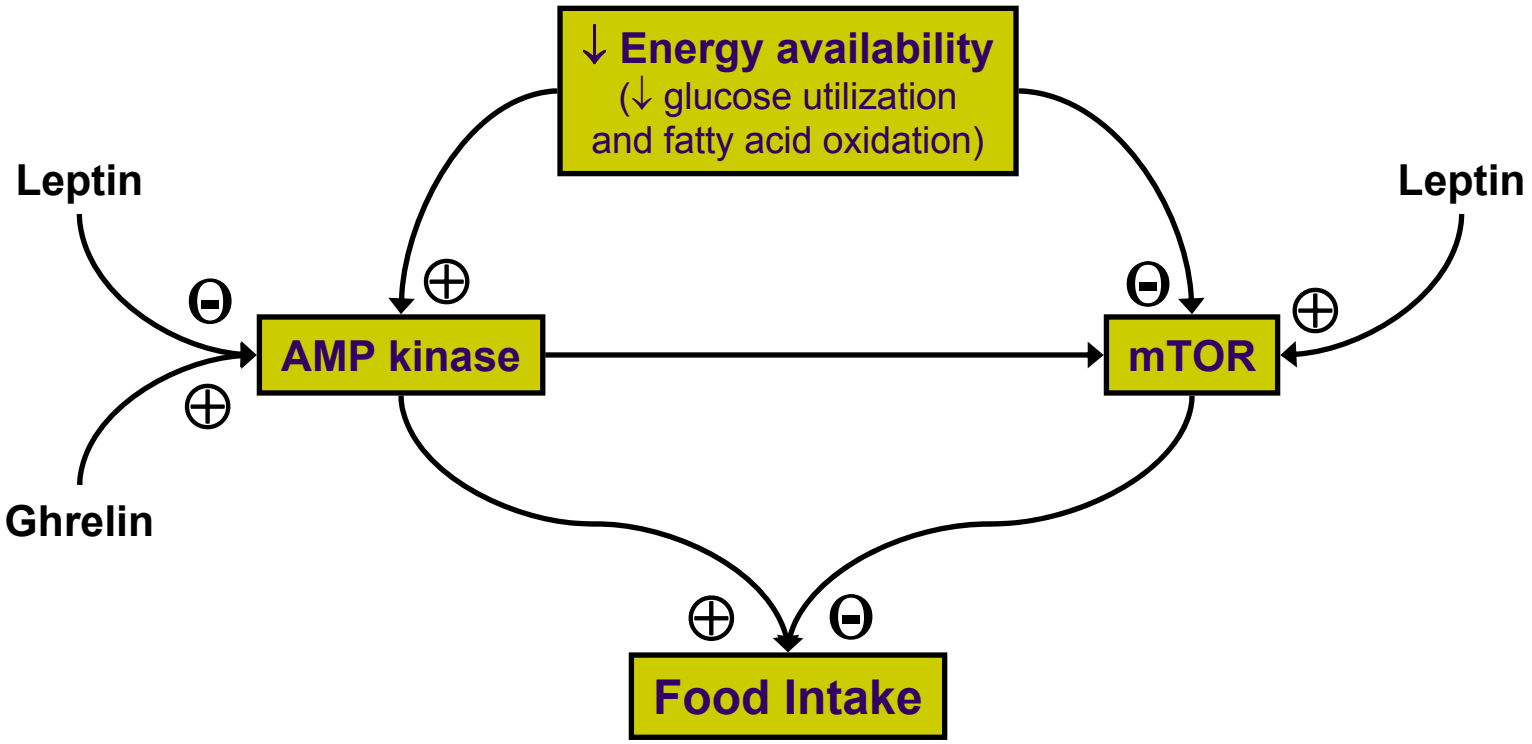


Regulation of hypothalamic AMPK by hormonal and nutrient signals



(Kahn et al., Cell Metabol. 1:15-25, 2005)

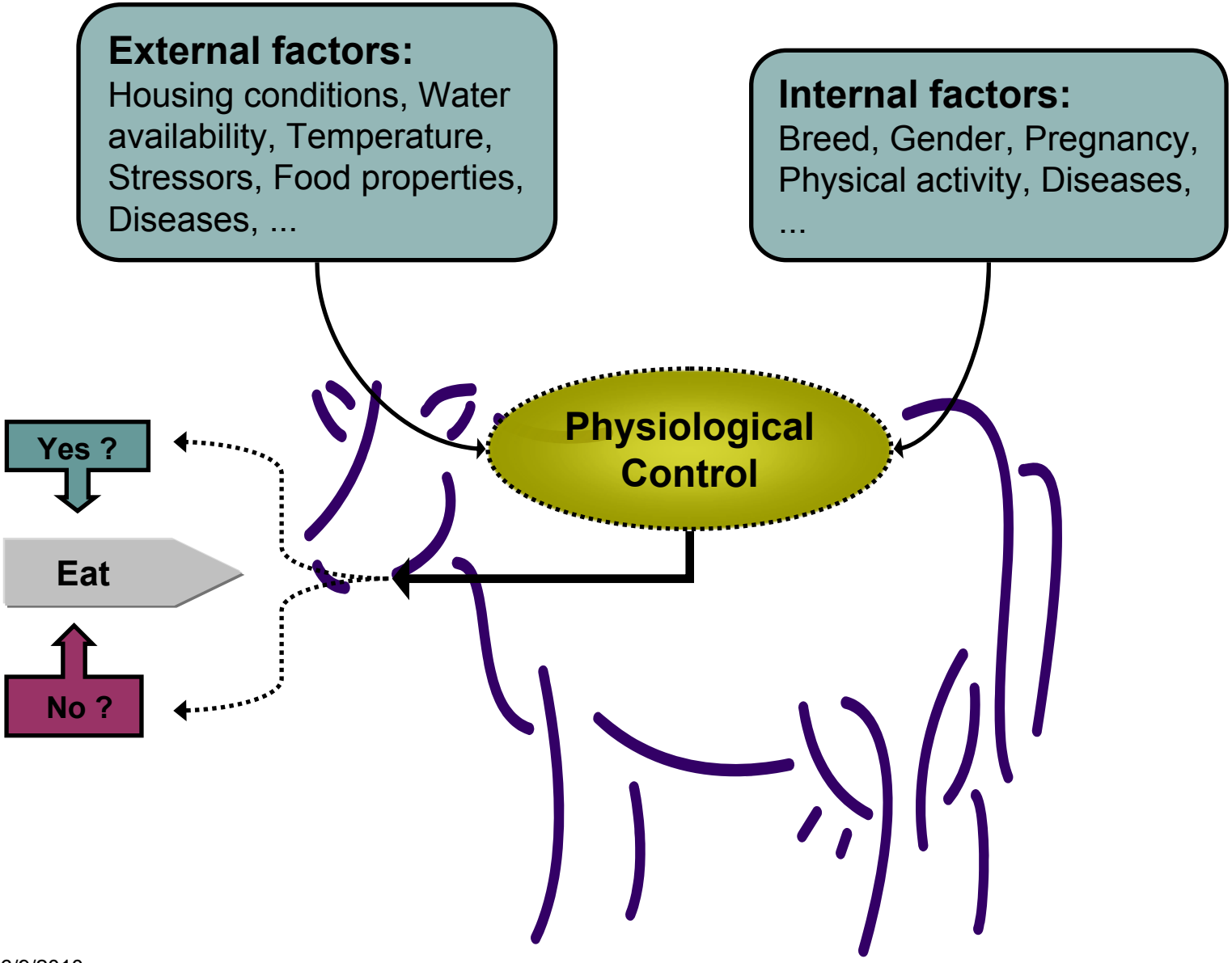
Crosstalk between AMPK und mTOR in the hypothalamic control of hunger and satiety



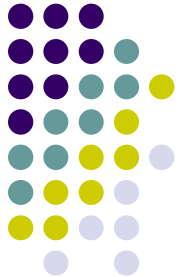
mTOR = mammalian target of rapamycin

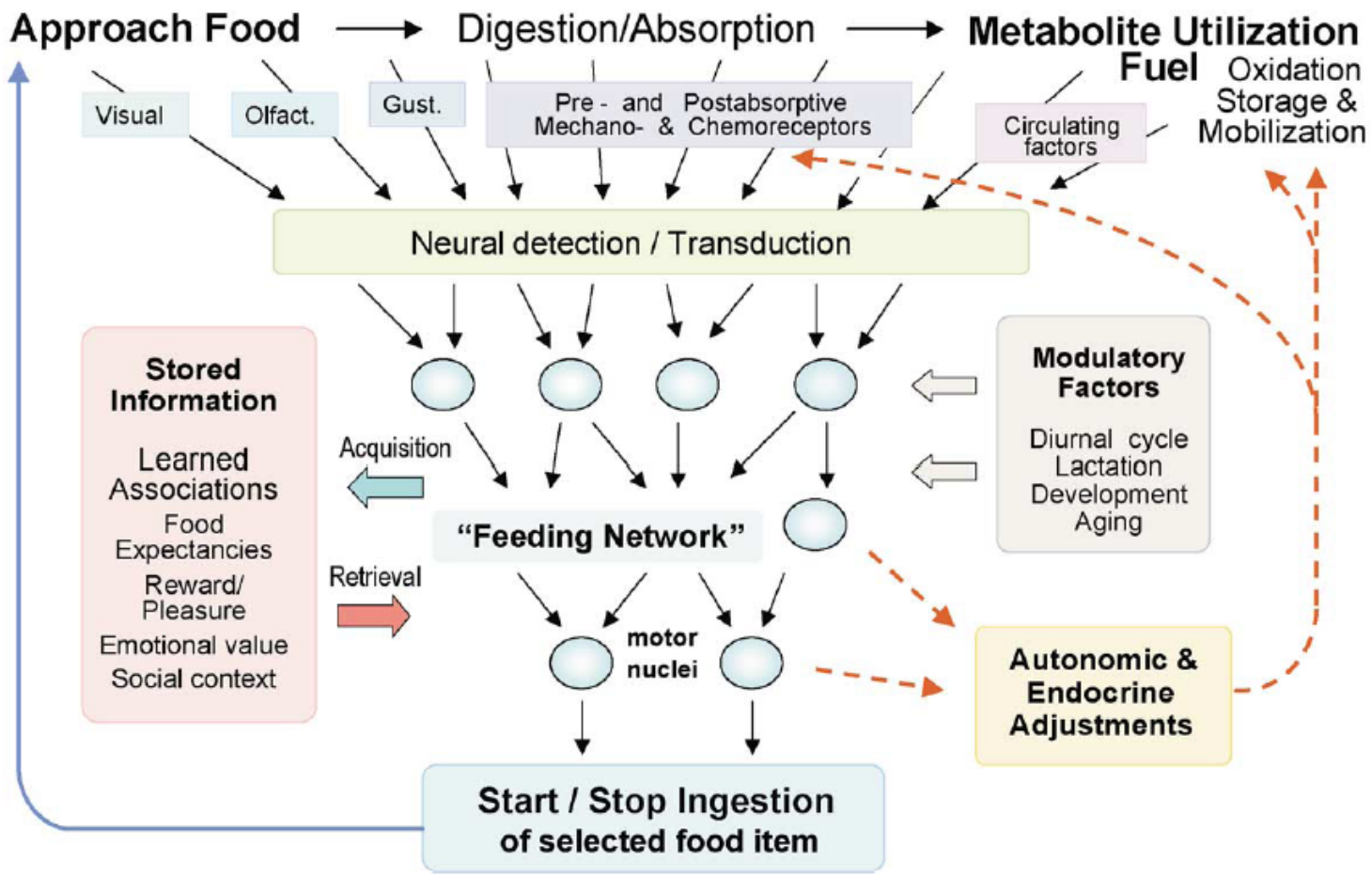
Verzehrsregulation

- Allgemeines
- Steuerung von Mahlzeitgrösse und -frequenz
- Adipositassignale
- Zentralnervöse Mechanismen
- **Äussere und innere Faktoren**


External factors:
Housing conditions, Water availability, Temperature, Stressors, Food properties, Diseases, ...
Internal factors:
Breed, Gender, Pregnancy, Physical activity, Diseases, ...
Physiological Control
Yes ?
Eat
No ?


Thank you for
your attention !

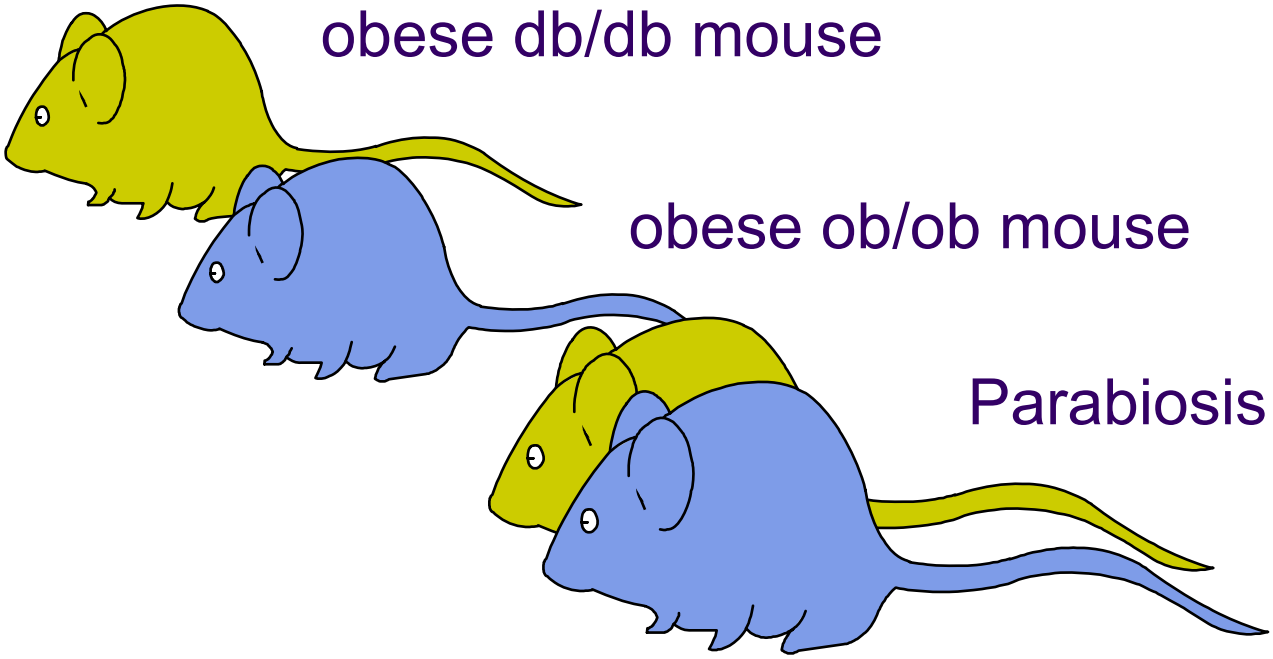



H.-R. Berthoud / Neuroscience and Biobehavioral Reviews 26 (2002) 393–428
Approach Food
Digestion/Absorption
Metabolite Utilization
Fuel
Oxidation
Storage &
Mobilization
Visual
Olfact.
Gust.
Pre - and Postabsorptive
Mechano- & Chemoreceptors
Circulating
factors
Neural detection / Transduction
Stored
Information
Learned
Associations
Food
Expectancies
Reward/
Pleasure
Emotional value
Social context
Acquisition
Retrieval
"Feeding Network"
motor
nuclei
Modulatory
Factors
Diurnal cycle
Lactation
Development
Aging
Autonomic &
Endocrine
Adjustments
Start / Stop Ingestion
of selected food item

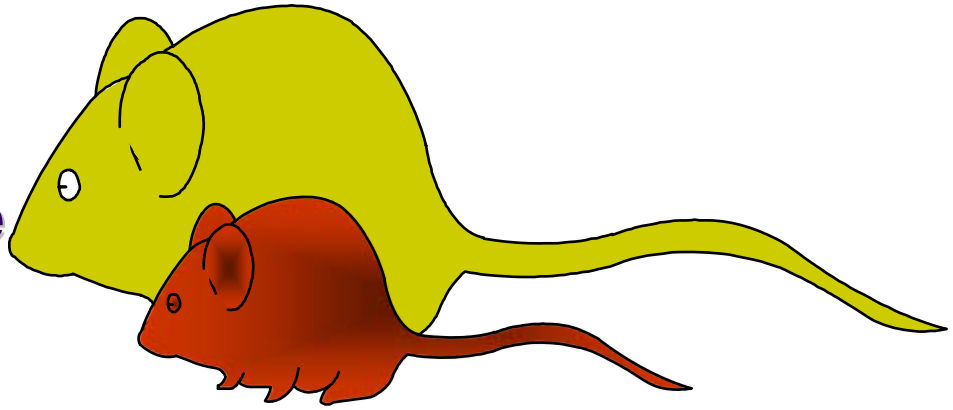
obese db/db mouse

obese ob/ob mouse

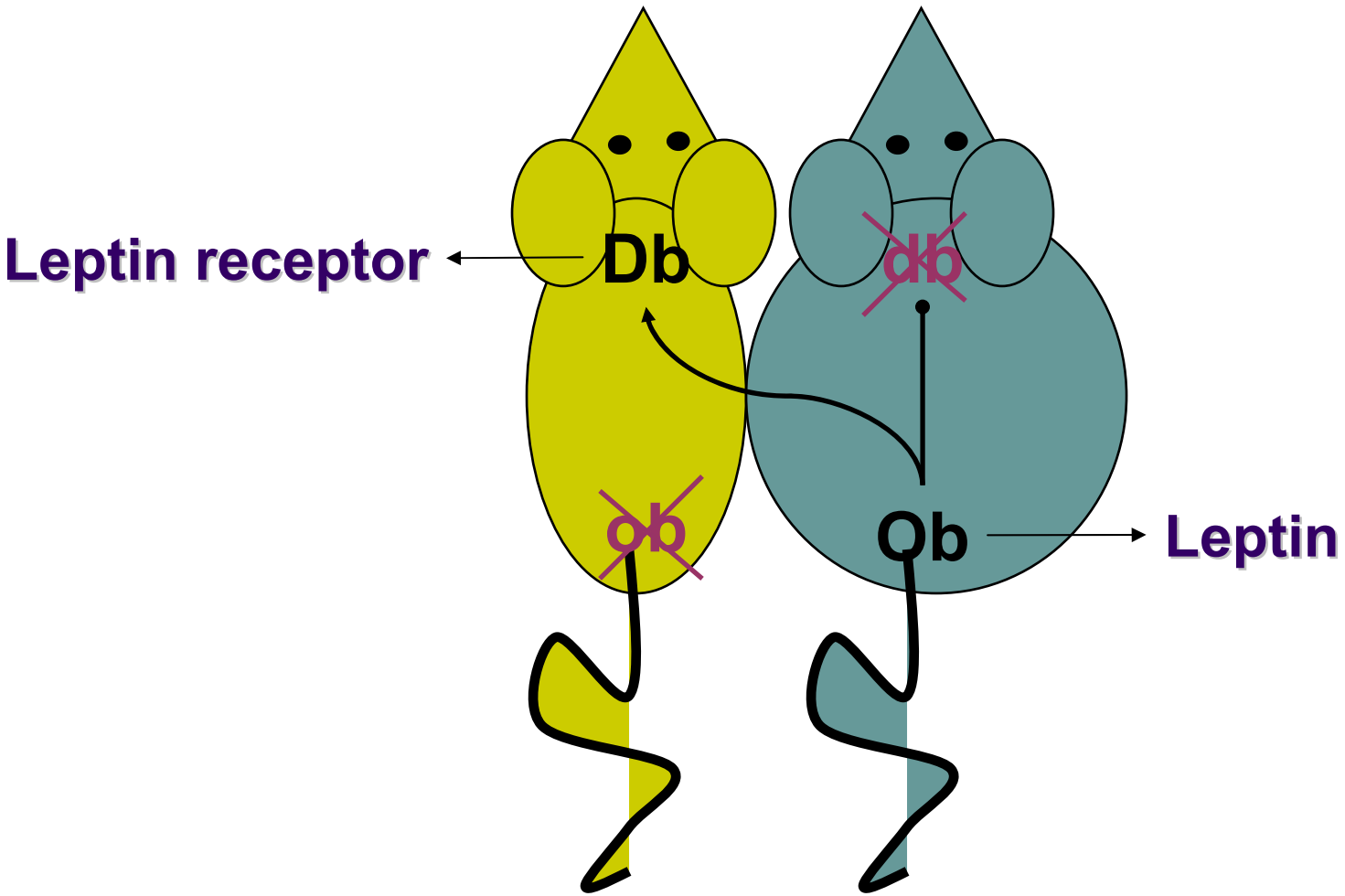
Parabiosis



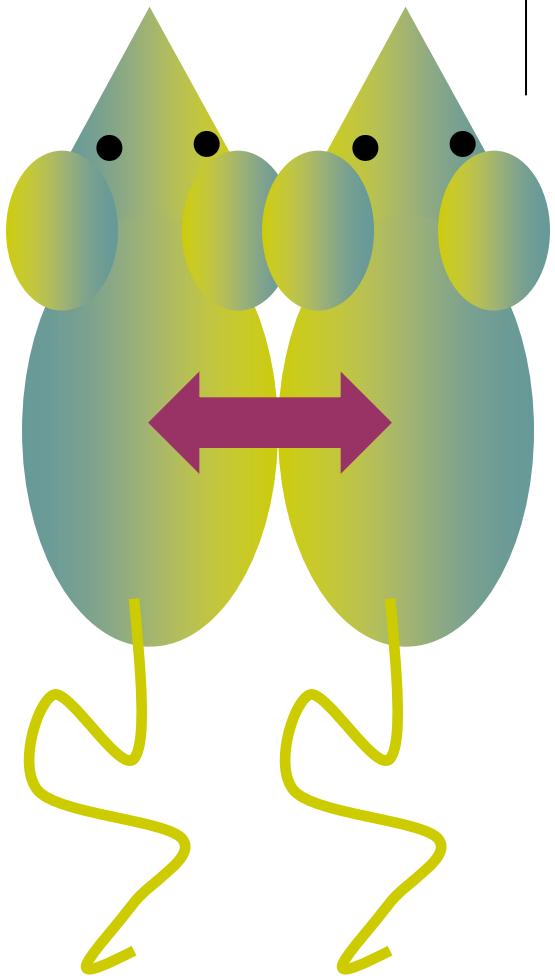
ob/ob mouse stops eating



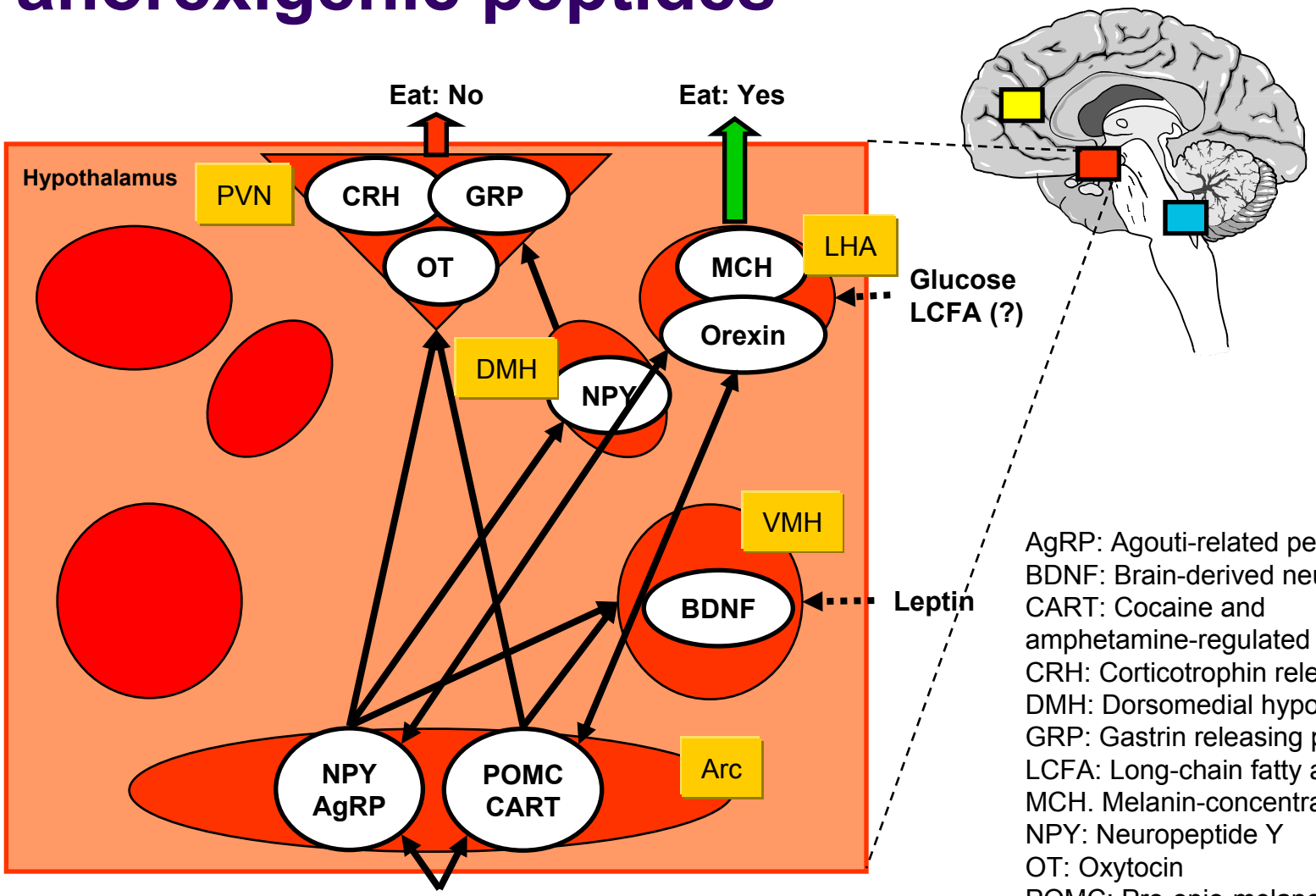
(Coleman 1973)


Leptin receptor
Db
db
ob
Ob
Leptin

Cross-perfusion studies and parabiosis experiments indicate that **body fat affects eating and metabolism through a blood-borne factor**

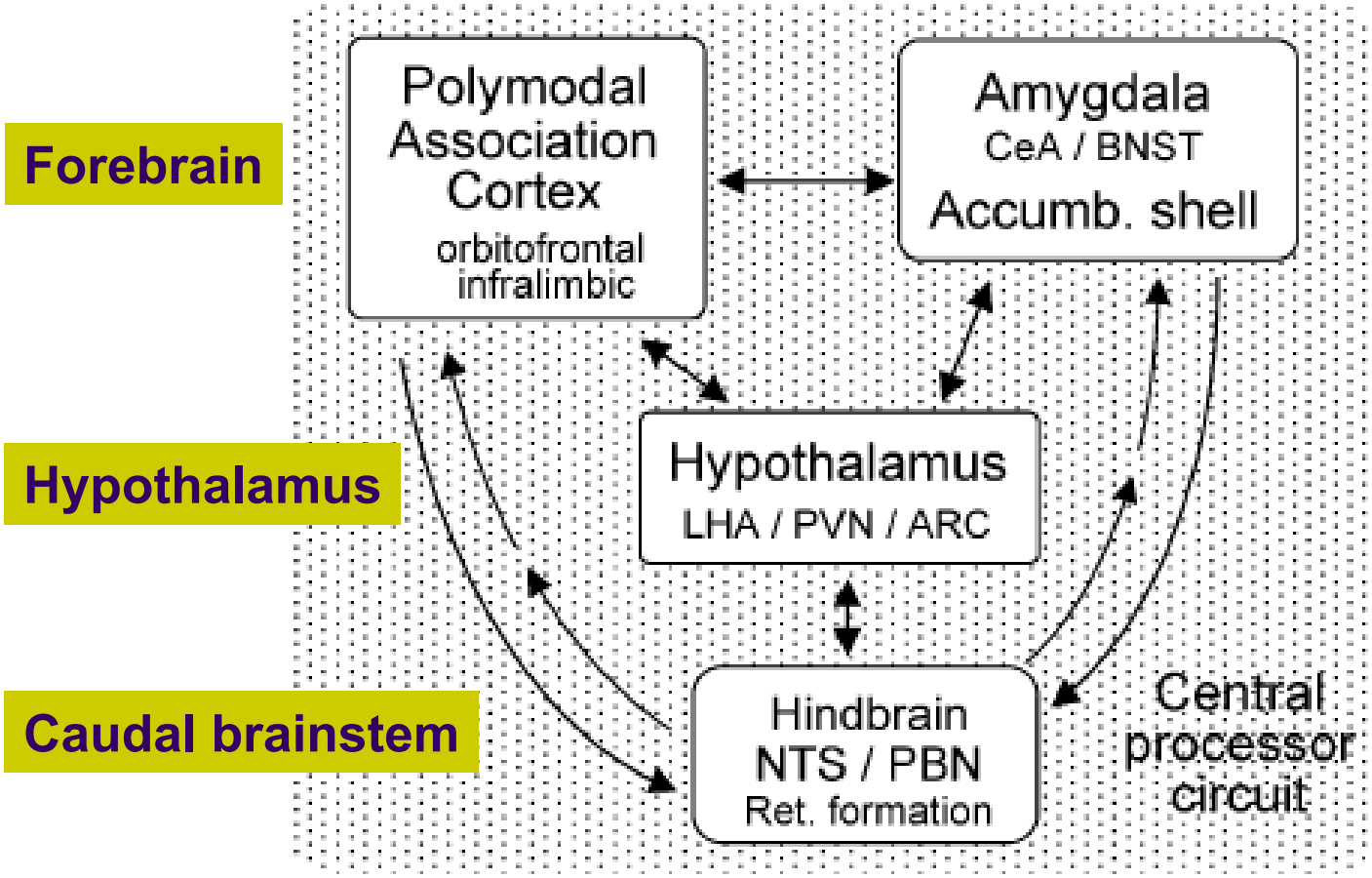


Hypothalamus with orexigenic and anorexigenic peptides



AgRP: Agouti-related peptide
BDNF: Brain-derived neurotropic factor
CART: Cocaine and amphetamine-regulated transcript
CRH: Corticotrophin releasing hormone
DMH: Dorsomedial hypothalamus
GRP: Gastrin releasing peptide
LCFA: Long-chain fatty acids
MCH. Melanin-concentrating hormone
NPY: Neuropeptide Y
OT: Oxytocin
POMC: Pro-opio-melanocortin
PYY: Peptide YY

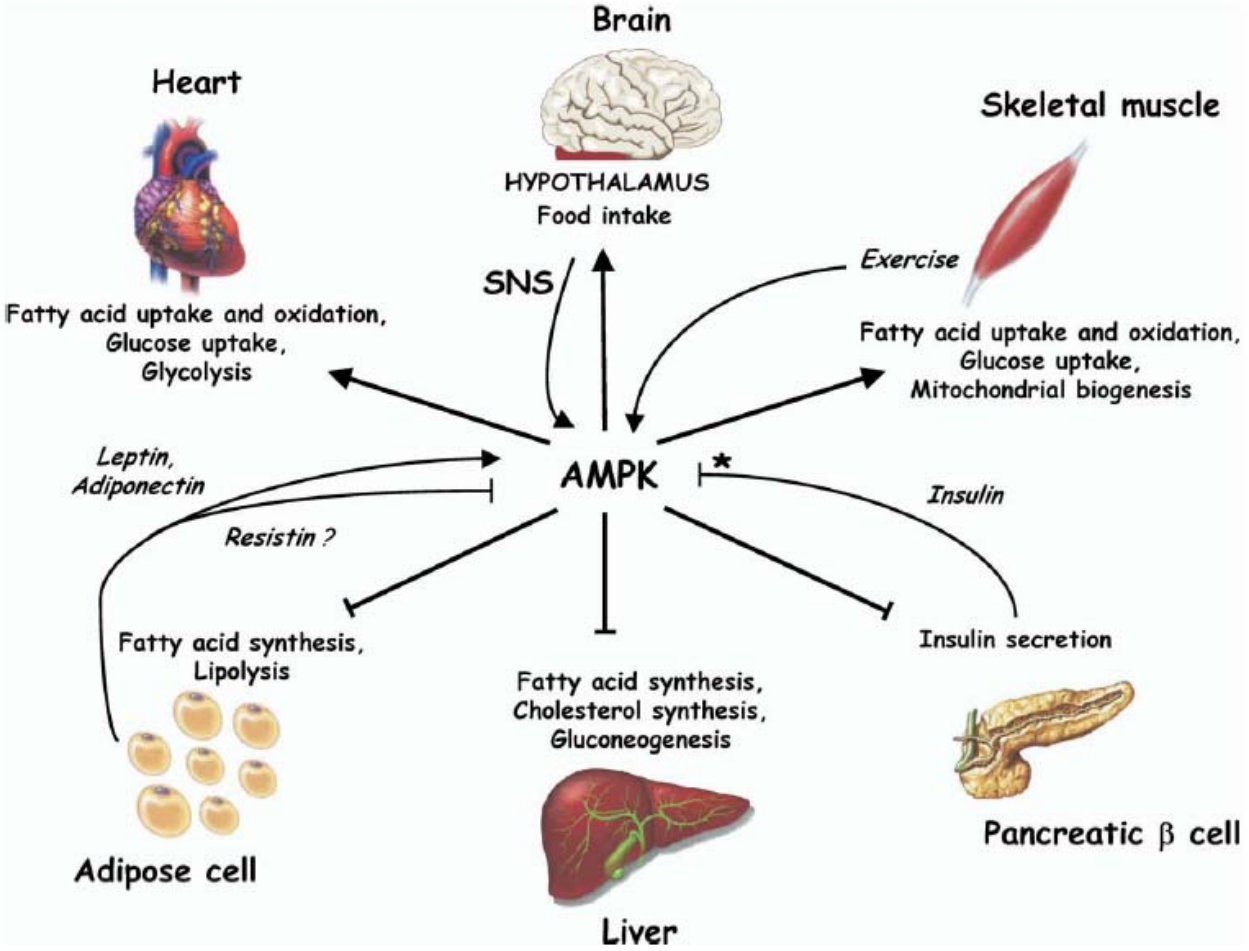
Major nodes in the central nervous system control of eating



The central processor circuit includes at least certain areas in the cortex, amygdala, hypothalamus, and caudal medulla. At least some of the subnuclei within these four brain areas exhibit direct reciprocal anatomical connections with each other, thus allowing rapid and continuous information exchange.

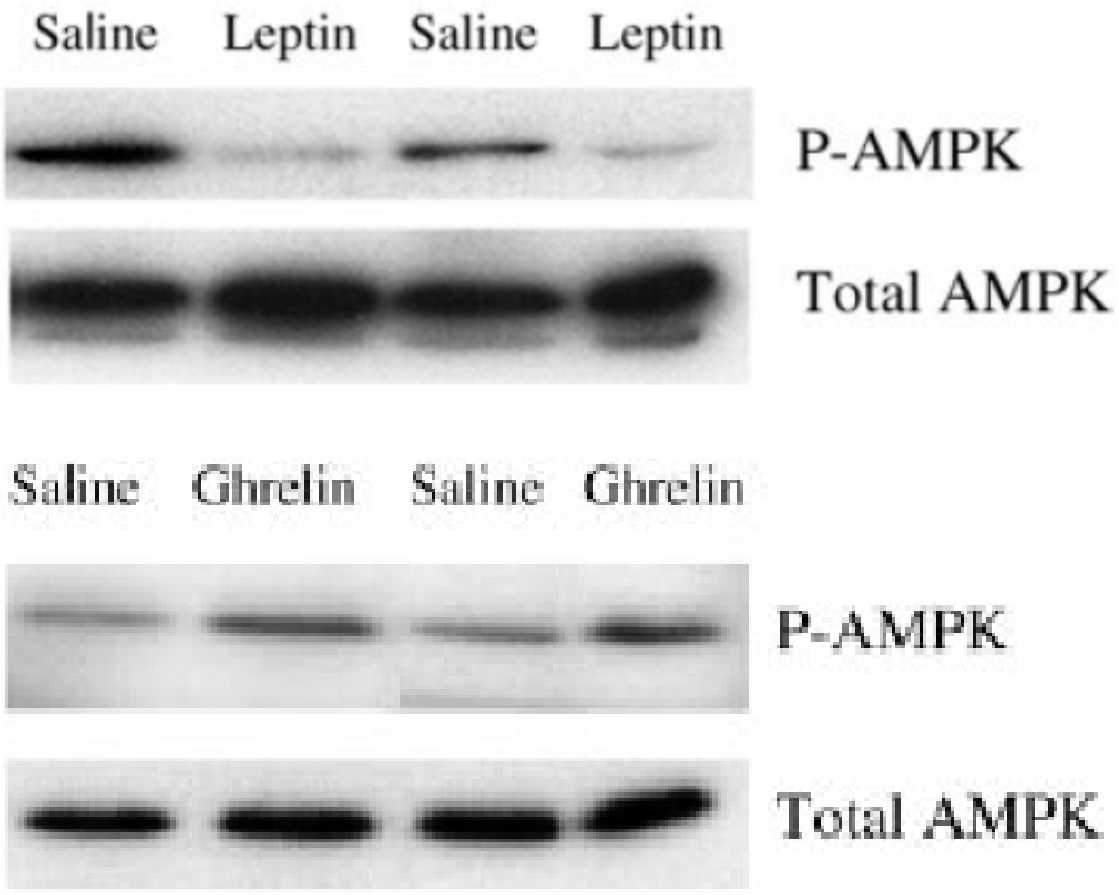
(Berthoud, Neurosci. Biobehav. Rev. 26: 393-428, 2002)

The AMP-activated protein kinase (AMPK) is an ubiquitous sensor of cellular energy status



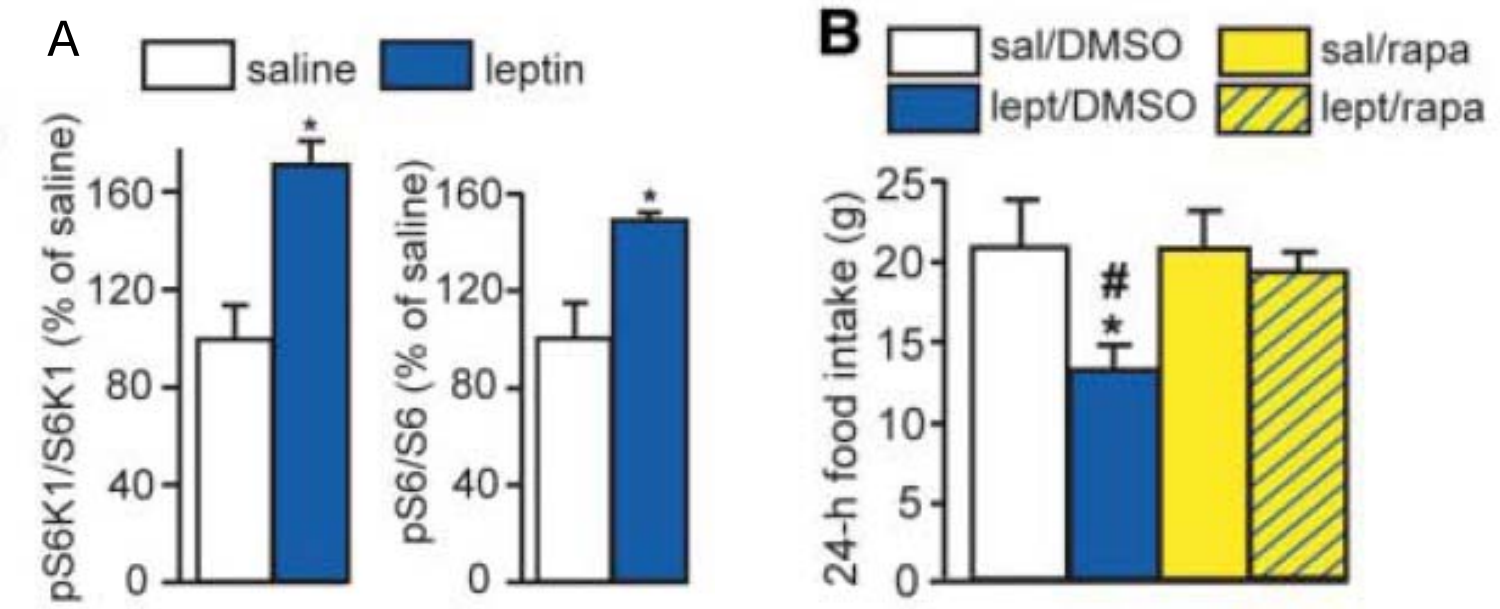
(Kahn et al., Cell Metabol. 1:15-25, 2005)

P-AMPK in the hypothalamus is reduced by leptin and increased by ghrelin



Andersson et al., J. Biol. Chem. 279:12005-12008, 2004

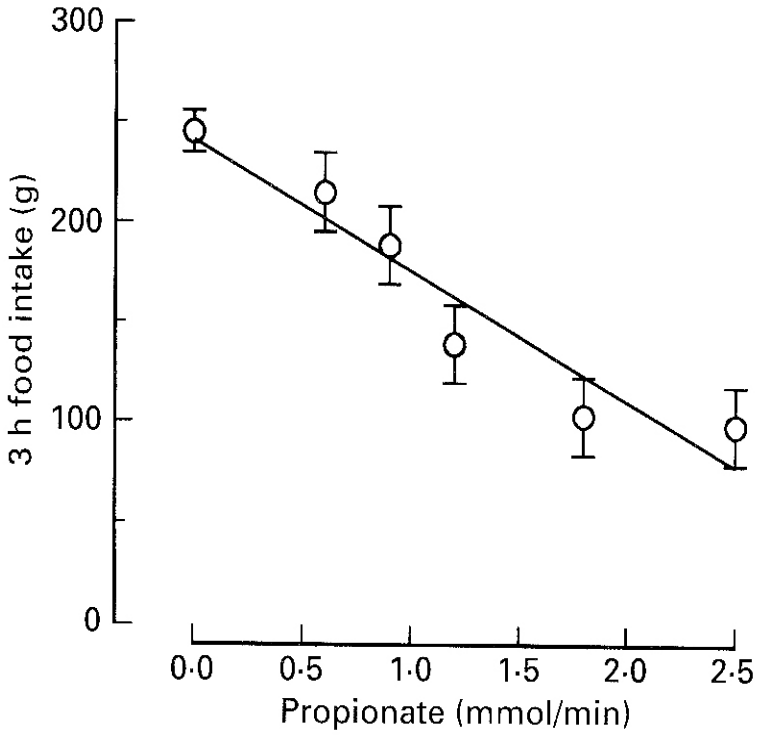
Leptin increases hypothalamic mTOR activity (A) and reduces food intake through activating mTOR (B)



(Cota et al., Science 312:927-930, 2006)

mTOR = mammalian target of rapamycin

Effect of 3 h IV propionate infusion on food intake in sheep



(Farningham & Whyte, Br. J. Nutr. 70:37-46, 1993)

Factors that affect rumen fill:

- Particle size
- Chewing frequency and effectiveness
- Particle fragility
- Indigestible NDF fraction
- Rate of fermentation of potentially digestible NDF
- Characteristics of reticulo-ruminal contractions

(Allen, J. Anim. Sci. 74:3063-3075, 1996)