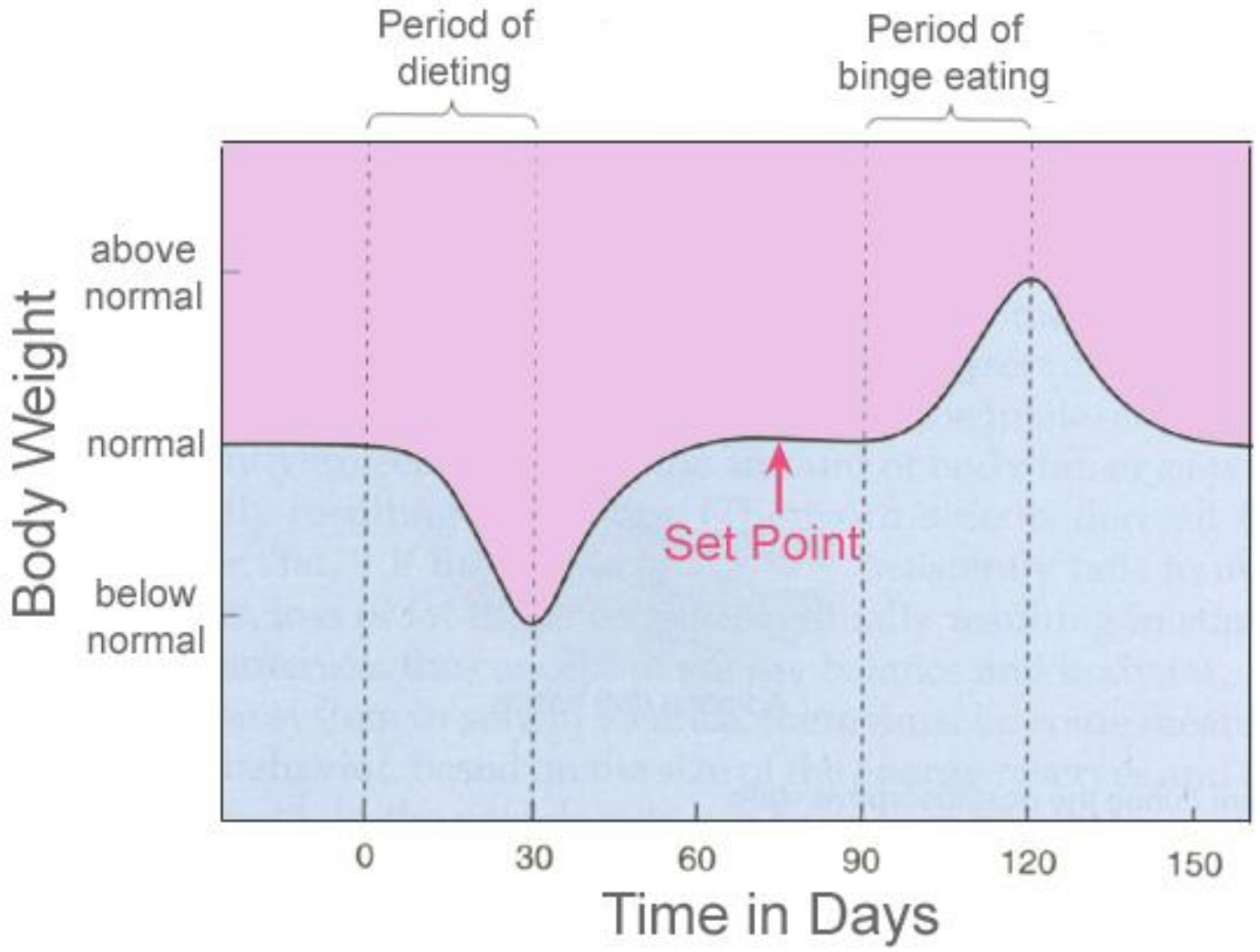
Regulation of food consumption and energy surplus



Advantages of keeping steady levels of energy sources.
Not less, not more.

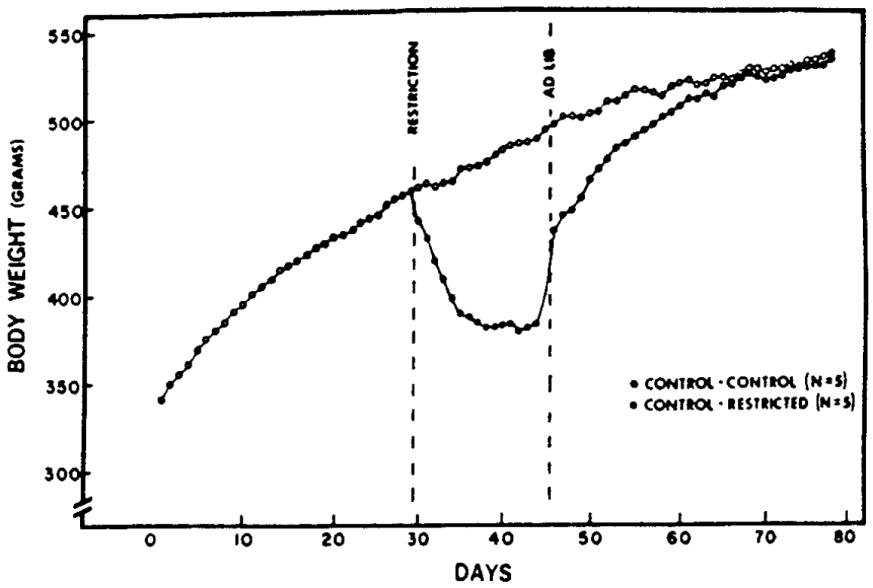
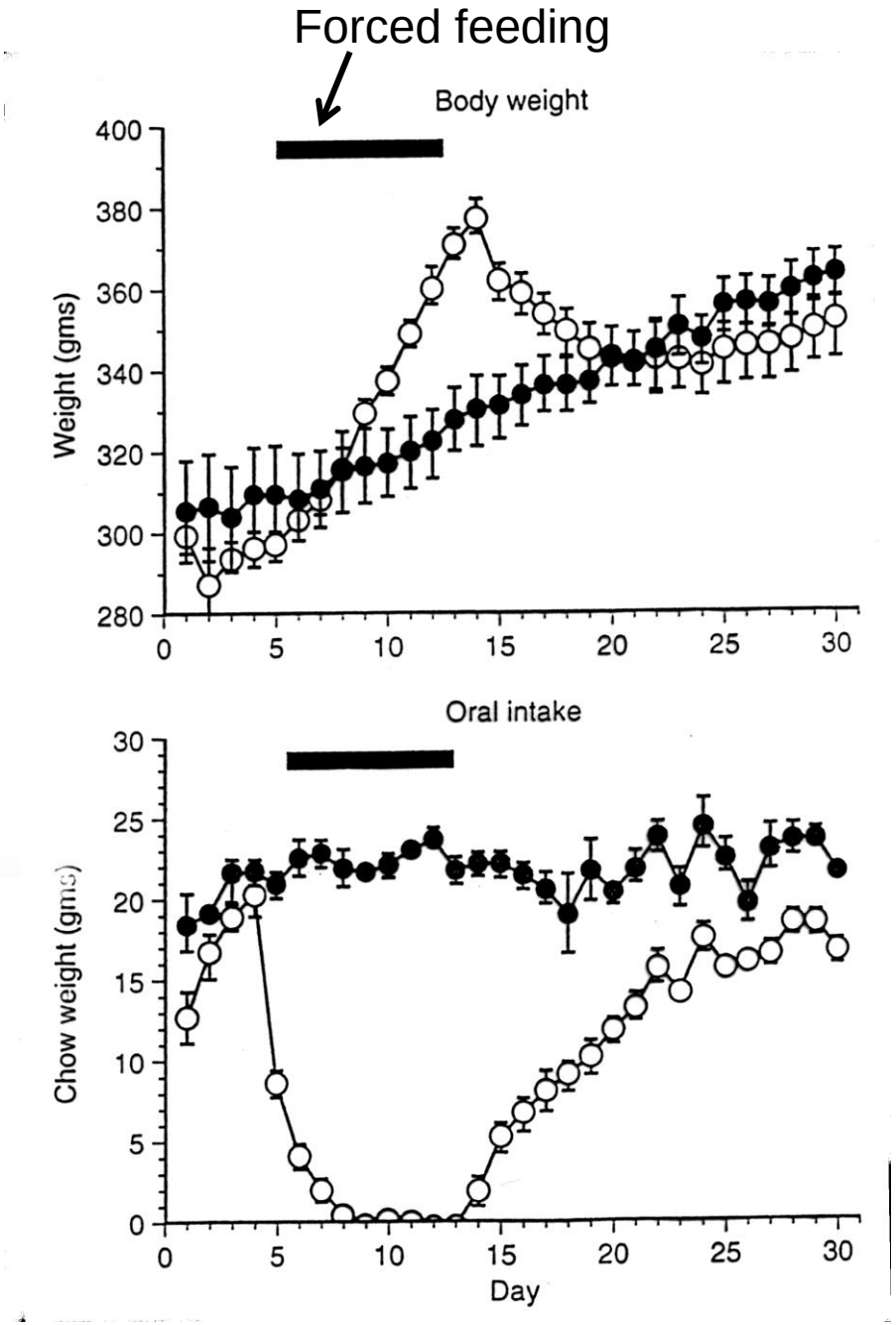
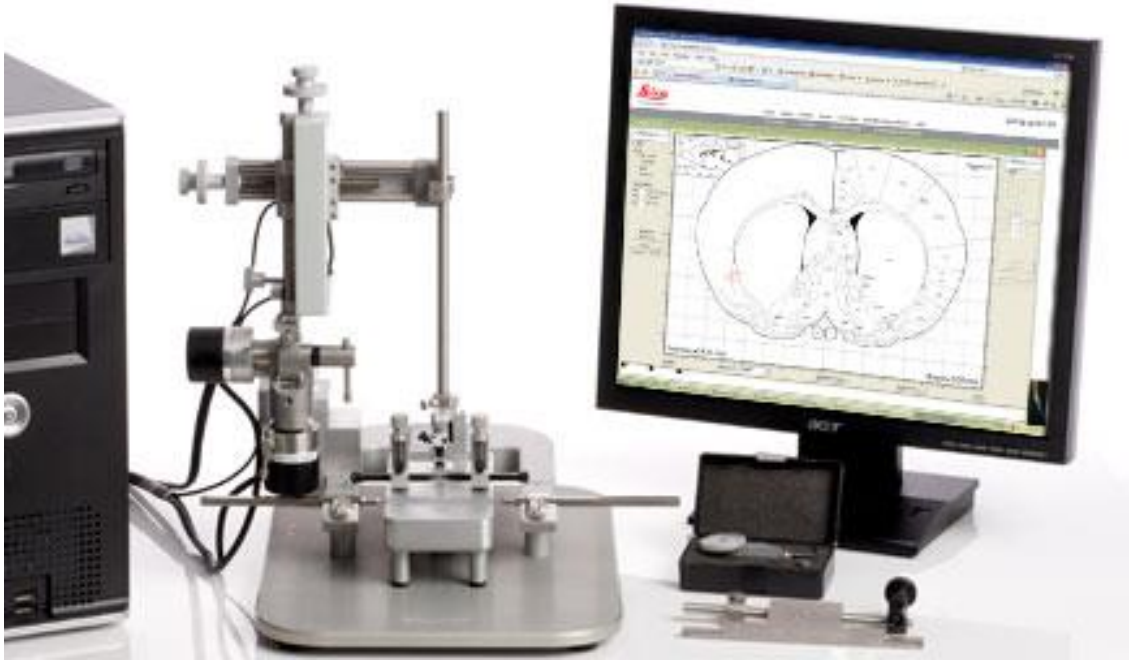


FIGURE 1 Recovery of body weight by rats after a period of caloric restriction [adapted with permission from Mitchel and Keesey (1977)].



	Kcal/gr	gr/Kcal
Fat	9.4	0.11
Protein	4.3	0.23
Carbohydrate	4.2	0.24
Glycogen	1.0	1.00



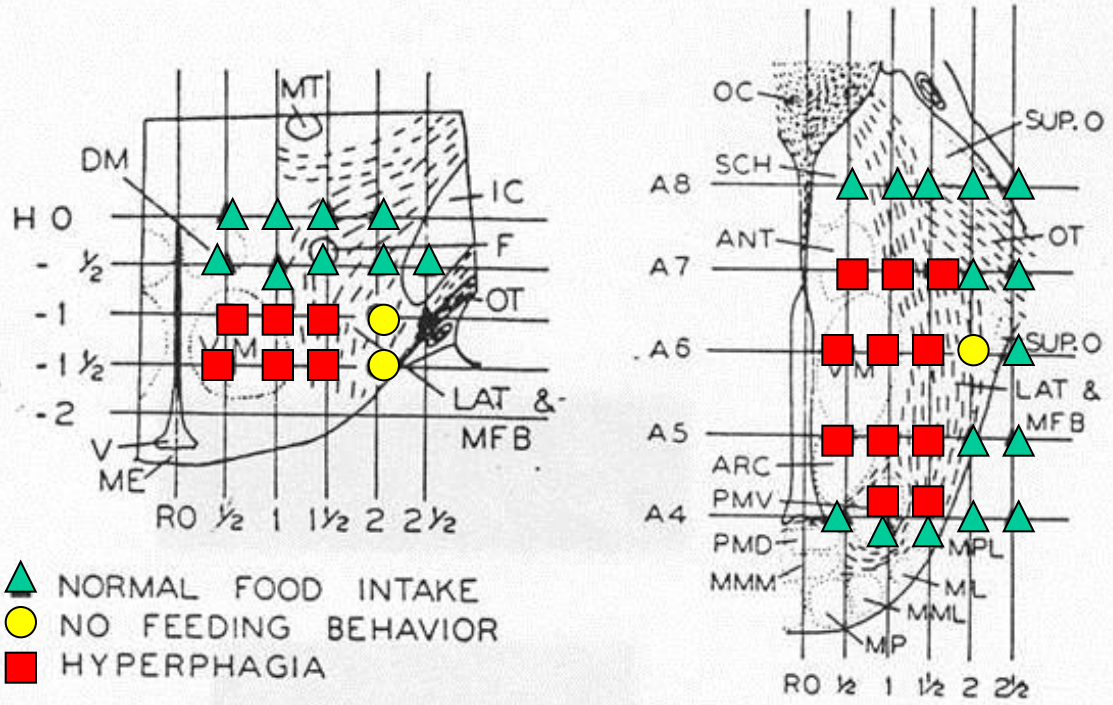
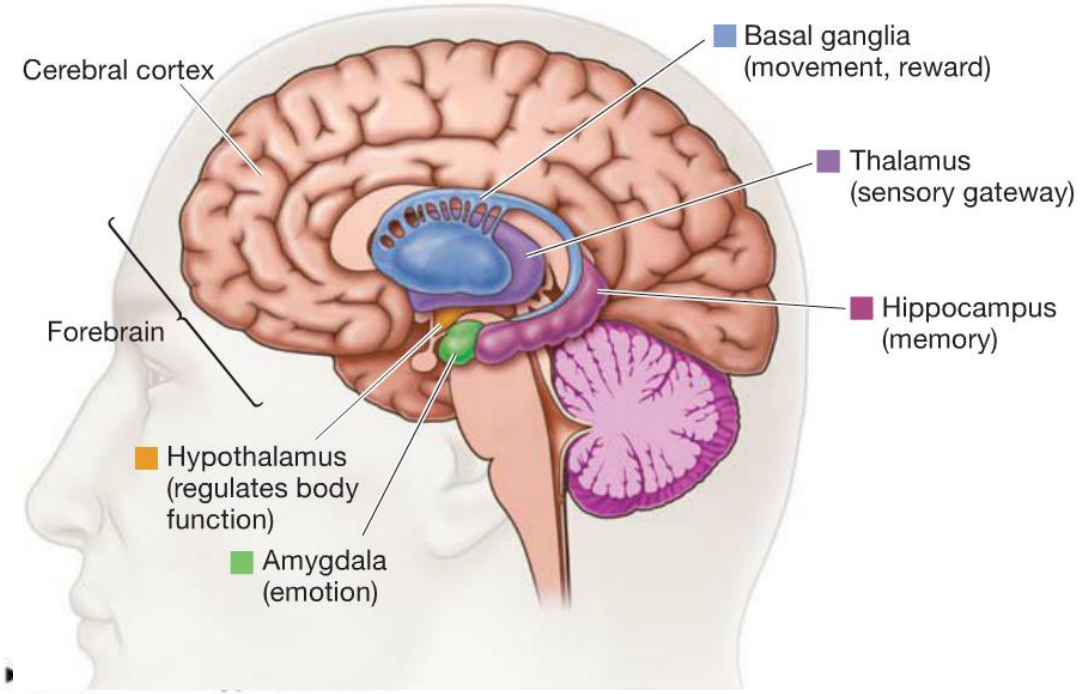
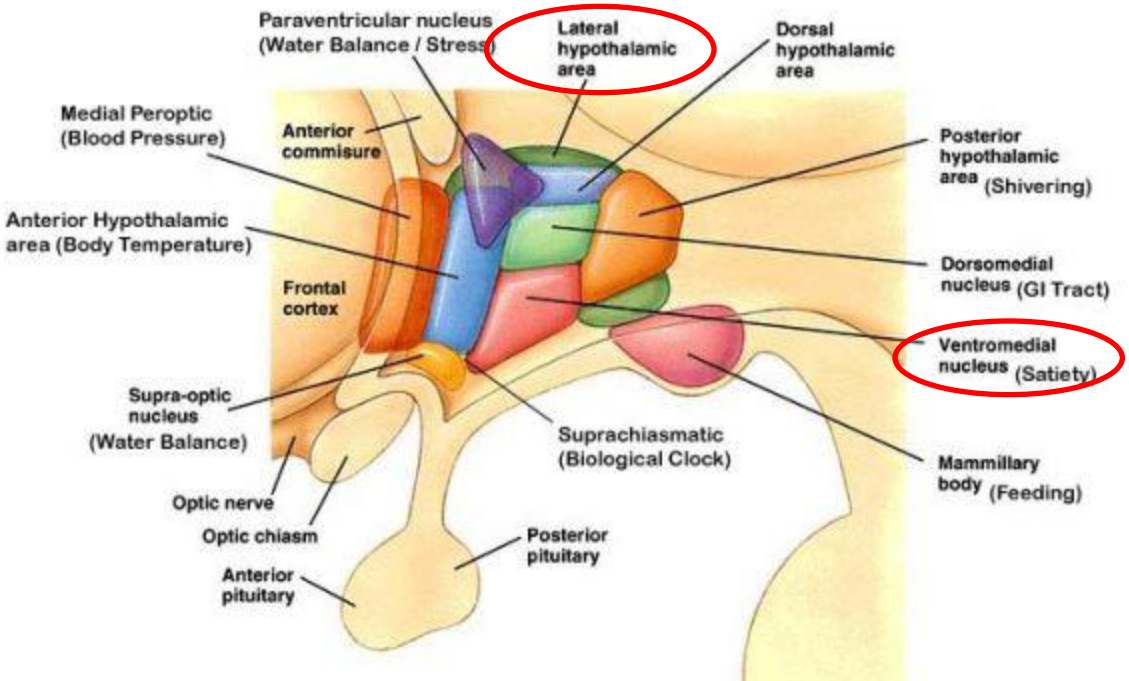
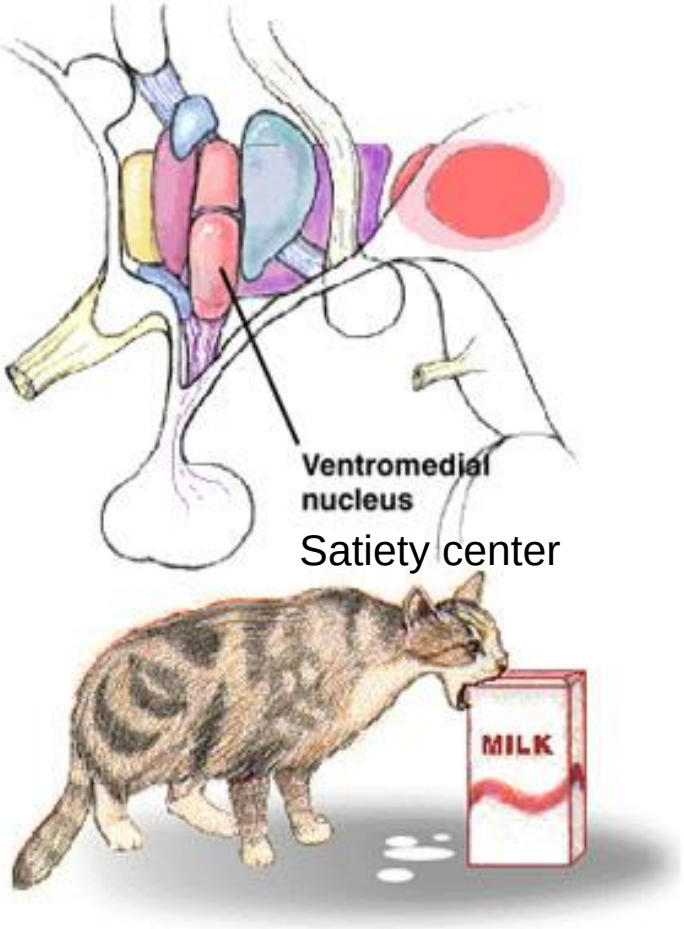


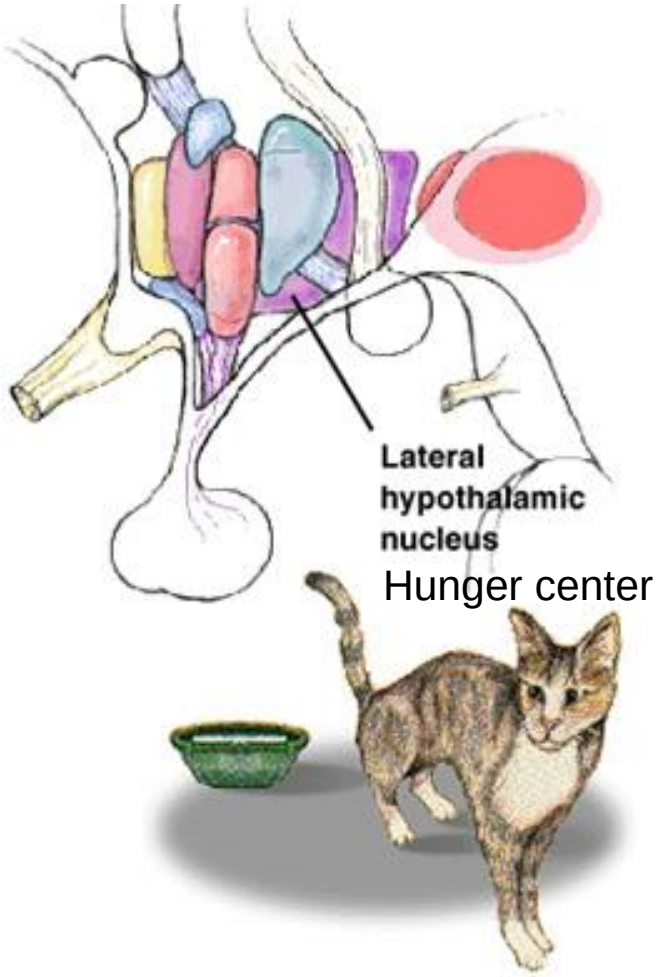
FIGURE 15-4. Cross section of a rat's hypothalmus at level of the ventromedial nucleus (*left*) and of the same side in a horizontal plane, also at the level of the ventromedial nucleus (*right*). Horsley-Clarke coordinates are superimposed. The feeding behavior of rats with small bilaterally symmetrical lesions in each area is indicated. (From Anand and Brobeck,[16] courtesy of *Yale J. Biol. Med.*)


Cerebral cortex
Basal ganglia
(movement, reward)
Thalamus
(sensory gateway)
Hippocampus
(memory)
Forebrain
Hypothalamus
(regulates body
function)
Amygdala
(emotion)


Paraventricular nucleus
(Water Balance / Stress)
Lateral
hypothalamic
area
Dorsal
hypothalamic
area
Medial Peroptic
(Blood Pressure)
Anterior
commisure
Posterior
hypothalamic
area (Shivering)
Anterior Hypothalamic
area (Body Temperature)
Dorsomedial
nucleus (GI Tract)
Frontal
cortex
Ventromedial
nucleus (Satiety)
Supra-optic
nucleus
(Water Balance)
Suprachiasmatic
(Biological Clock)
Mammillary
body (Feeding)
Optic nerve
Optic chiasm
Posterior
pituitary
Anterior
pituitary



Satiety center



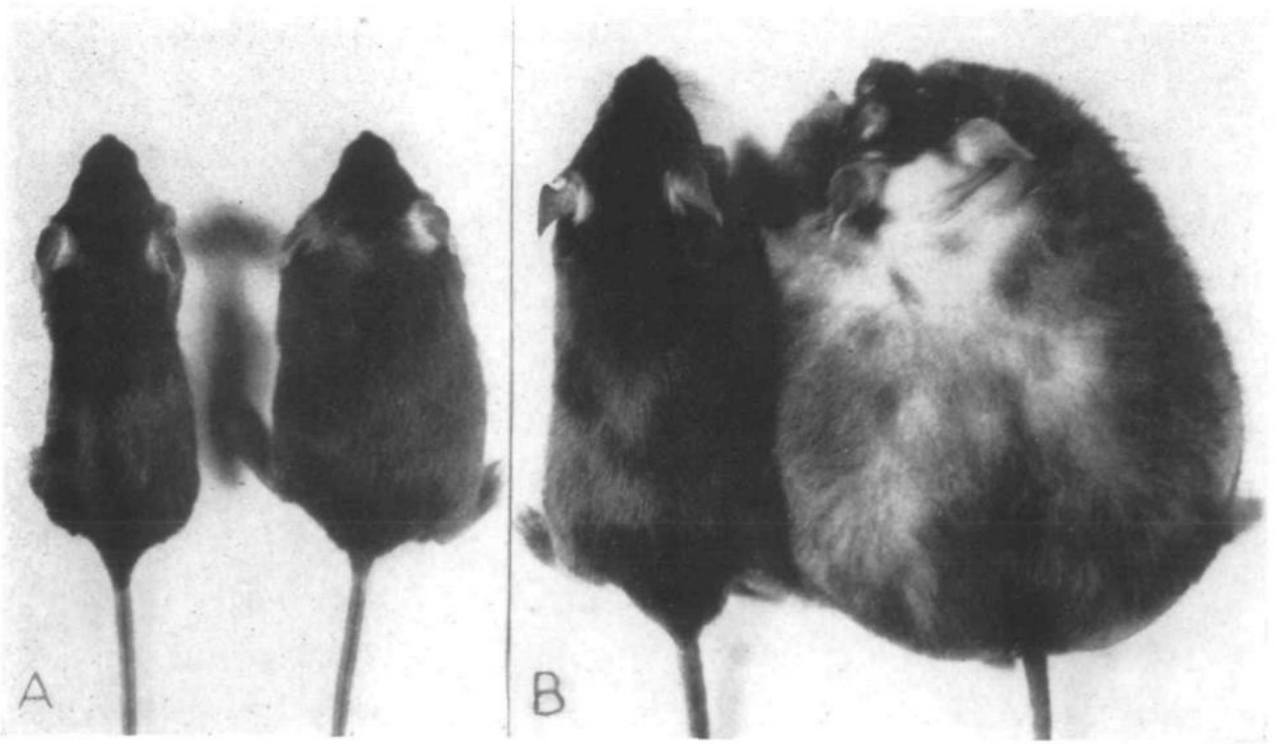
Hunger center

The **lipostatic hypothesis**. Body weight and fat mass stays constant by hypothalamic control. The hypothalamus senses to the concentration of a metabolites in the circulation and regulates the amount of energy surplus.

Kennedy, 1953

OBESE, A NEW MUTATION IN THE HOUSE MOUSE*

ANN M. INGALLS, MARGARET M. DICKIE AND G. D. SNELL
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine



THE FAT MOUSE GROWS UP

Figure 4

A—shows normal control and an obese mouse at 21 days of age. The former weighed 12 grams; the latter 16. *B* shows a normal and obese mouse at ten months of age, when the obese mouse weighed 90 grams and the normal mouse 29 grams.

The *ob* mutant is characterized by massive obesity, marked hyperphagia, mild diabetes and infertility

J Hered (1950)

db/db mutant mouse

The *db* (diabetes) mutant, like the *ob/ob* mouse, develops marked obesity and hyperphagia. It also develops severe, life-shortening diabetes.

Hummel (1966)

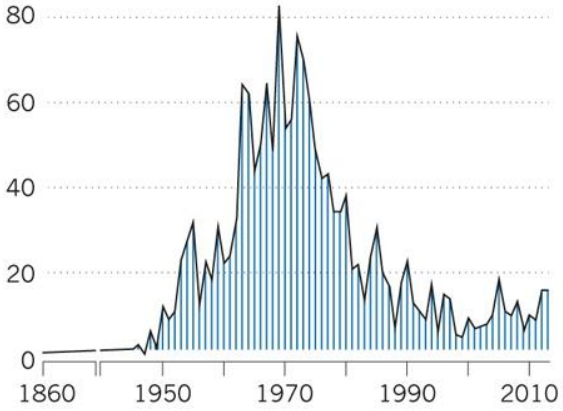
Parabiotic experiments

Share and share alike

Parabiotic experiments, in which two animals share a common bloodstream, were first attempted in the 1860s. By connecting animals with different qualities or conditions, scientists can investigate how blood factors, such as cells, proteins or hormones, influence health. In recent years, a few researchers have looked at heterochronic (old and young) mouse pairs to understand how young blood helps to repair many tissues.

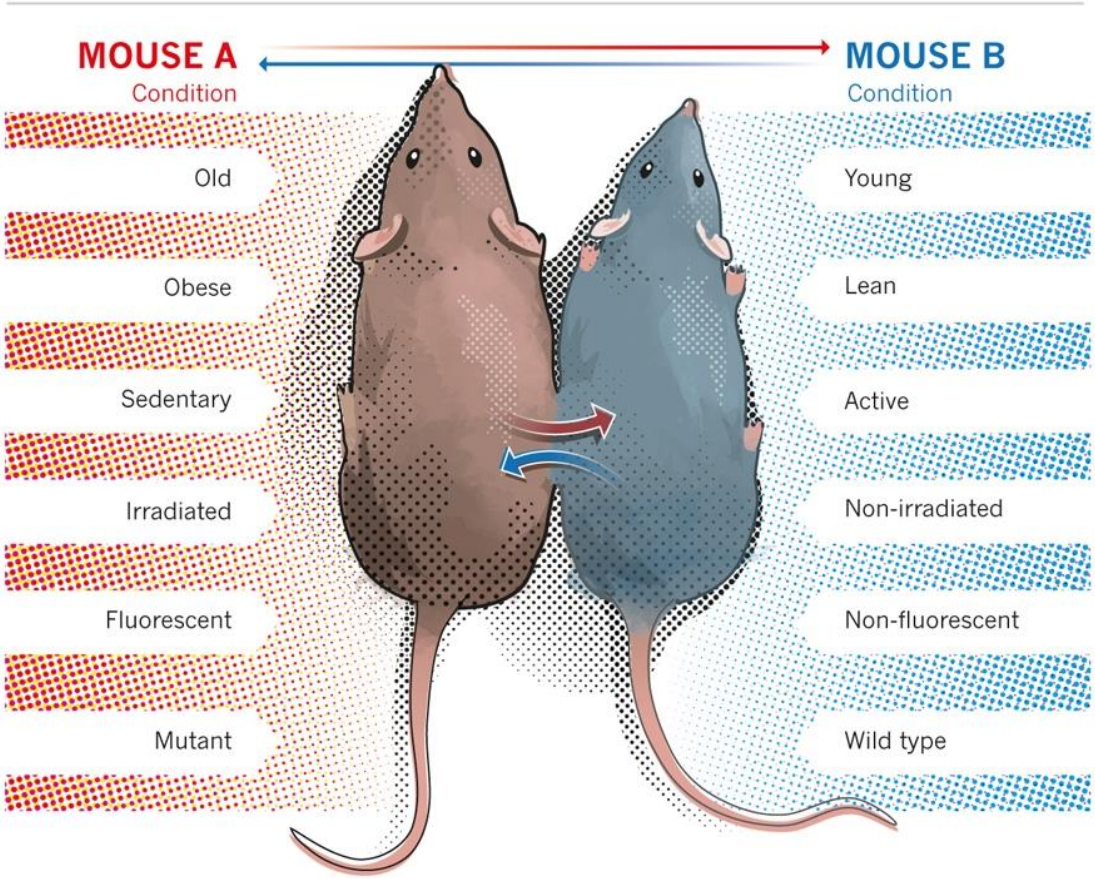
Publications on parabiosis

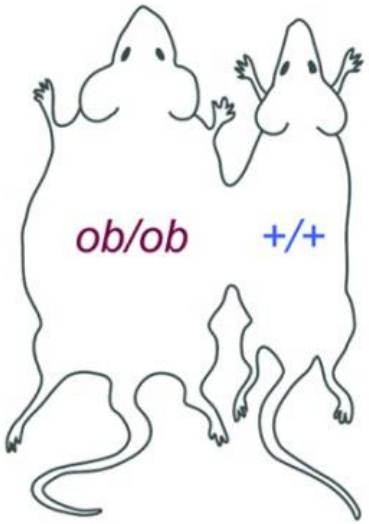
Parabiosis gained popularity during the 1960s and 1970s, but eventually fell out of wide practice.



A simple surgery

A veterinary surgeon will anaesthetize the animals, peel away a thin layer of skin along their sides and stitch or staple the exposed surfaces together. Wound-healing processes join the bloodstreams through a capillary network, and in one to two weeks, the animals are pumping each other's blood.



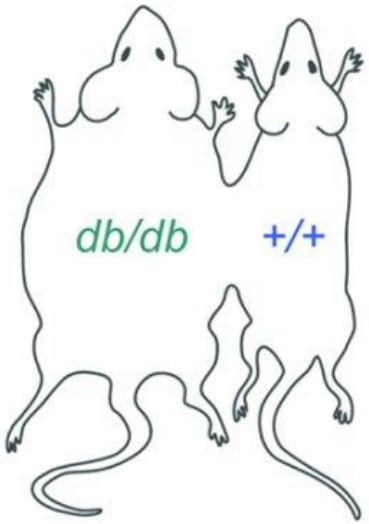


Obese

- ↓ Food intake
- ↓ Insulinemia
- ↓ Blood sugar

Wild type

No change



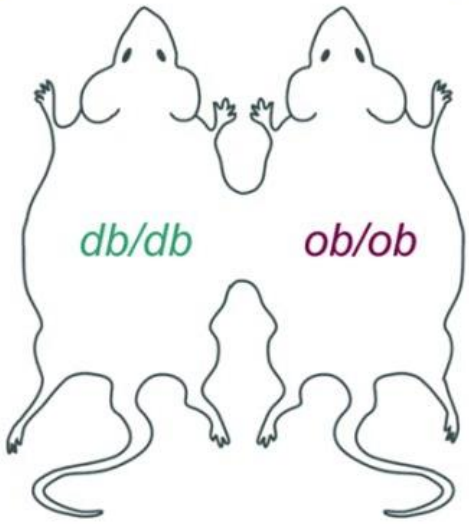
Diabetes

- ↑ Body weight
- ↑ Adipose tissue mass

Wild type

- ↓ Food intake
- ↓ Insulinemia
- ↓ Blood sugar

Death by starvation



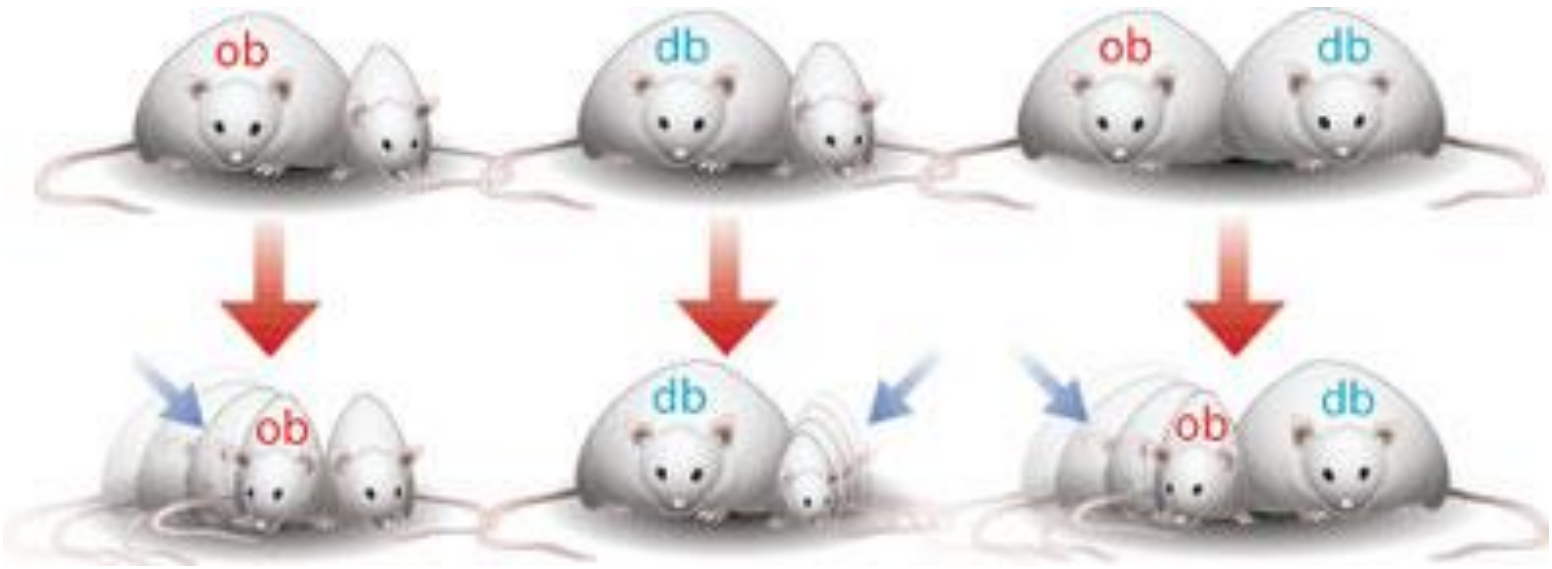
Diabetes

- ↑ Body weight
- ↑ Adipose tissue mass

Obese

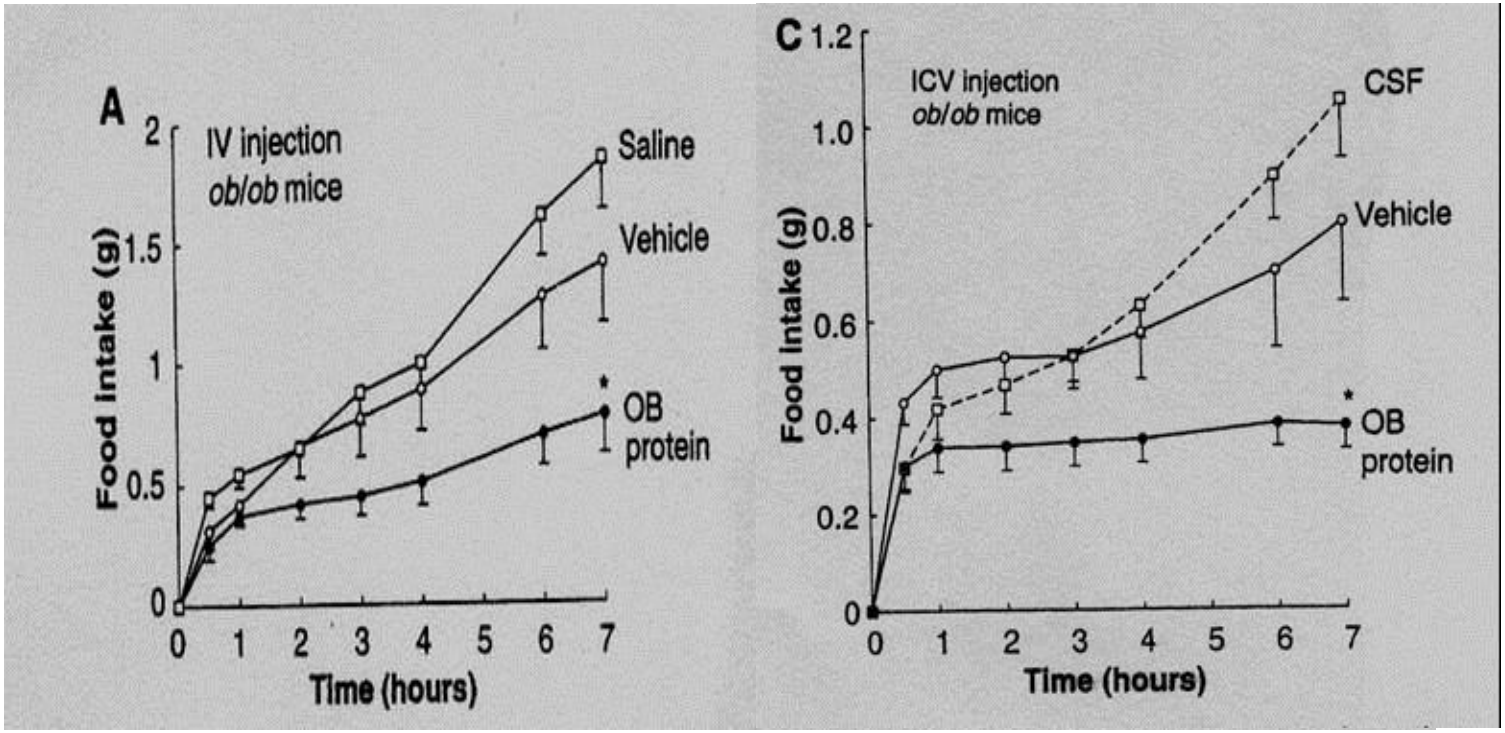
- ↓ Food intake
- ↓ Body weight
- ↓ Adipose tissue mass
- ↓ Insulinemia
- ↓ Blood sugar

Death by starvation

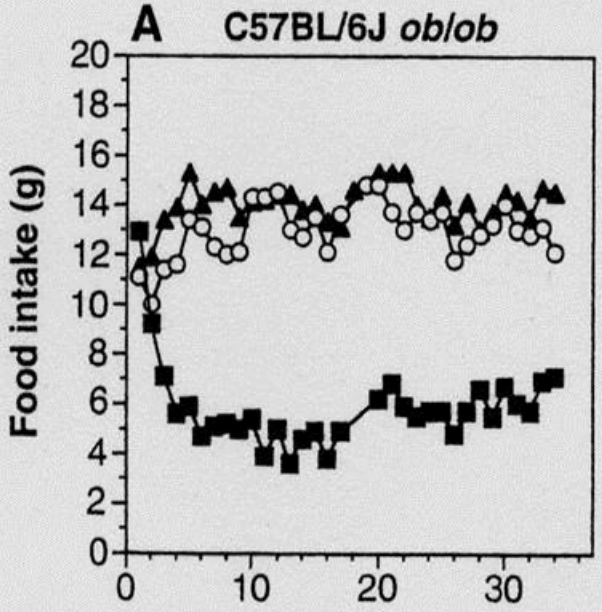


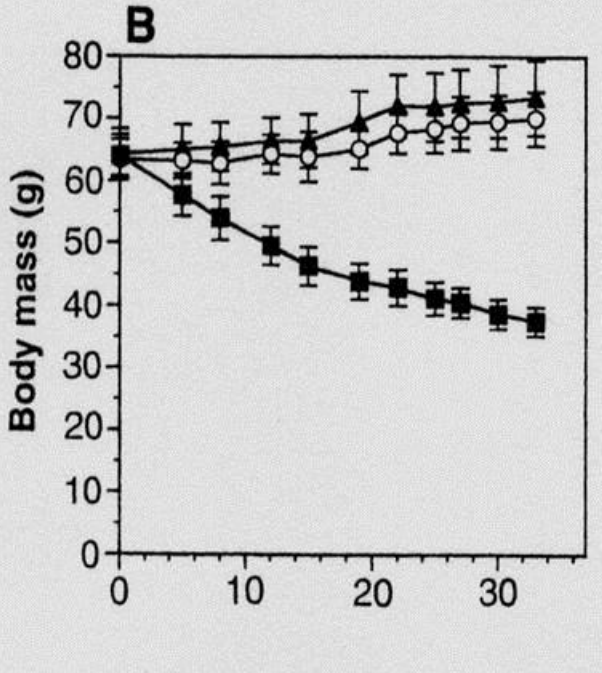
The ob/ob mice lucks the lipostatic factor and cannot control food intake.

The db/db mice has the lipostatic factor but does not respond to it because of a problem in the hypothalamic satiety center.
Coleman 1970



- One IV injection of leptin led to reduced food intake
- One ICV injection of leptin led to reduced food intake





■ 5μg leptin/day

○ PBS

▲ No injection

Leptin had an affect on food consumption and body mass of ob/ob

but had no effect on db/db


ob/ob, s.c. saline
ob/ob, s.c. leptin

Congenital leptin deficiency is associated with severe early-onset obesity in humans

Carl T. Montague*†, I. Sadaf Farooqi*†‡, Jonathan P. Whitehead*‡, Maria A. Soos*‡, Harald Rau*‡, Nicholas J. Wareham§, Ciaran P. Sewter*‡, Janet E. Digby*‡, Shehla N. Mohammed‖, Jane A. Hurst¶, Christopher H. Cheetham=, Alison R. Earley=, Anthony H. Barnett☆, Johannes B. Prins*‡ & Stephen O'Rahilly*‡

*University of Cambridge, Departments of * Medicine, ‡ Clinical Biochemistry and § Community Medicine, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QR, UK*

‖ South Thames Regional Genetics Centre (East), Guy's Hospital, London SE1 9RT, UK

¶ Oxford Regional Genetics Service, Churchill Hospital, Oxford OX3 7LJ, UK

= Wycombe General Hospital, Queen Alexandra Road, High Wycombe, Buckinghamshire HP11 2TT, UK

☆ Department of Medicine, University of Birmingham and Birmingham Heartlands Hospital, Birmingham B9 5SS, UK

† These authors contributed equally to this study.

A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction

Karine Clément*†‡, Christian Vaisse*†‡, Najiba Lahlou§, Sylvie Cabrol‖, Veronique Pelloux*, Dominique Cassuto*, Micheline Gourmelen‖, Christian Dina†, Jean Chambaz¶, Jean-Marc Lacorte¶, Arnaud Basdevant*†, Pierre Bougnères¶, Yves Lebouc‖, Philippe Froguel*† & Bernard Guy-Grand*†

* *Laboratoire de Nutrition et Service de Médecine et Nutrition, Hôtel-Dieu place du Parvis Notre Dame, 75004 Paris, France*

† *Institut de Biologie-CNRS EP10, Institut Pasteur de Lille, rue Calmette, 59000 Lille, France*

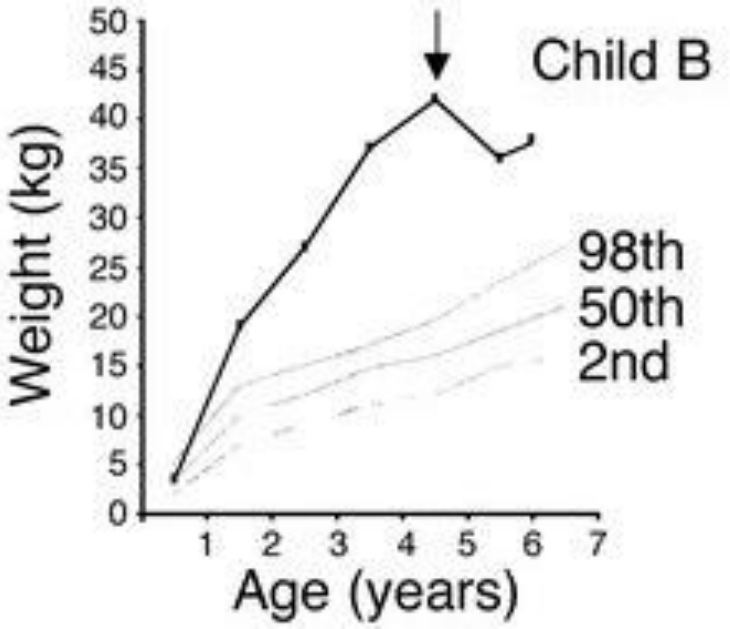
§ *Inserm U342, Hôpital Saint Vincent de Paul et service d'Endocrinologie-Diabète de l'Enfant, avenue Denfert Rochereau, 75014 Paris, France*

‖ *Explorations fonctionnelles endocriniennes, Hôpital d'enfant Armand Trousseau, avenue du Dr Arnold Netter, 75012 Paris, France*

¶ *CJF INSERM 9508, 15 rue de l'Ecole de Médecine, 75005 Paris, France*

‡ *These authors contributed equally to this work.*

Leptin deficiency

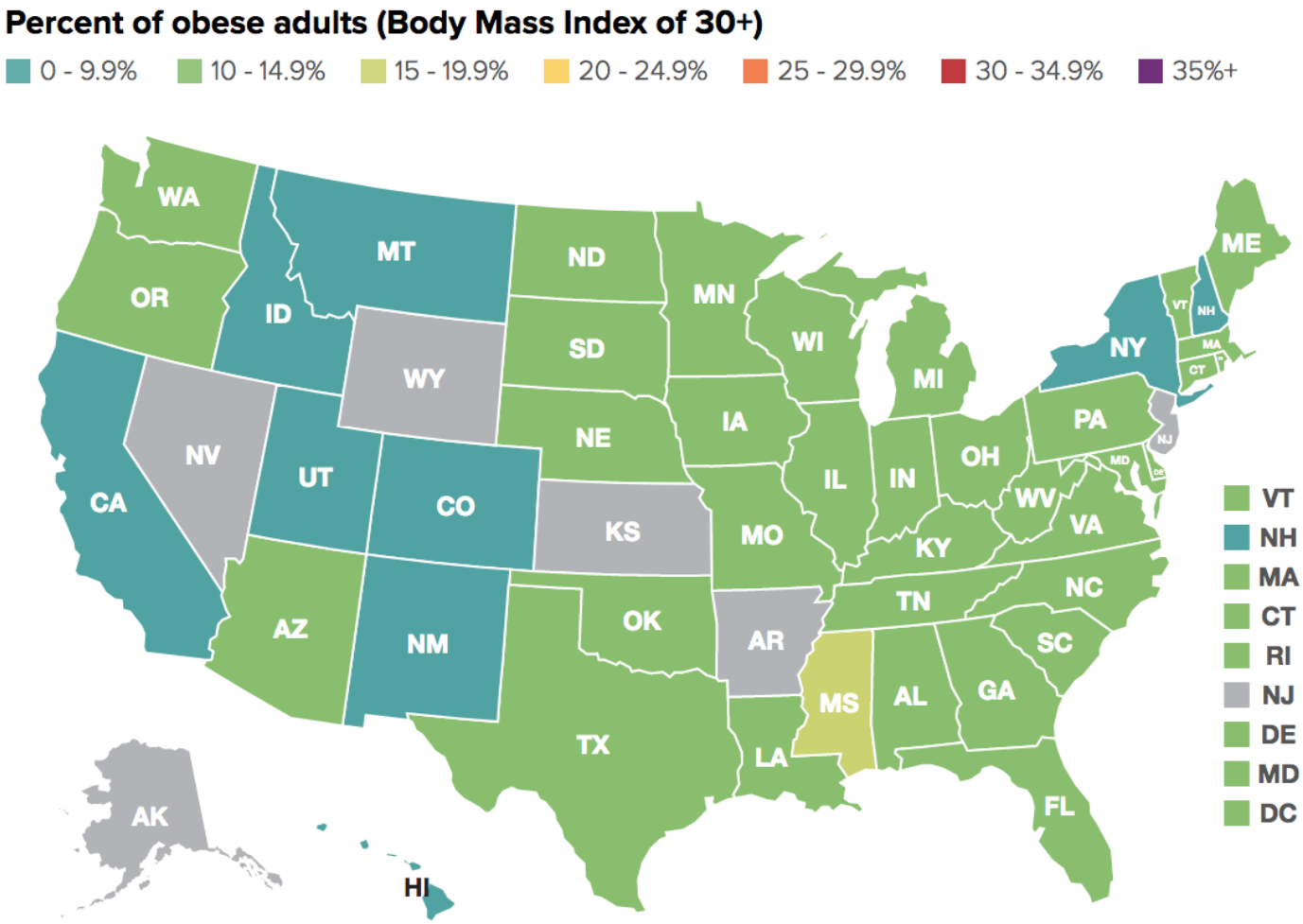


Clinical photographs of child B before and 24 months after Leptin therapy

J Clin Invest. 2002;110(8):1093-1103

Fig. 9 Leptin deficiency in humans responds to leptin treatment. A 3-year-old boy with congenital leptin deficiency with severe obesity (body weight 38 kg; BMI SD = 7.2) (left). On the right, the same patient, after four years of daily subcutaneous administration of recombinant leptin. Leptin treatment results in a dramatic decrease in adiposity (body weight 29 kg; BMI SD = 0.9) and normalization of all metabolic abnormalities including hyperinsulinaemia. Figure generously provided by Drs Sadaf Farooqi and Stephen O'Rahilly.

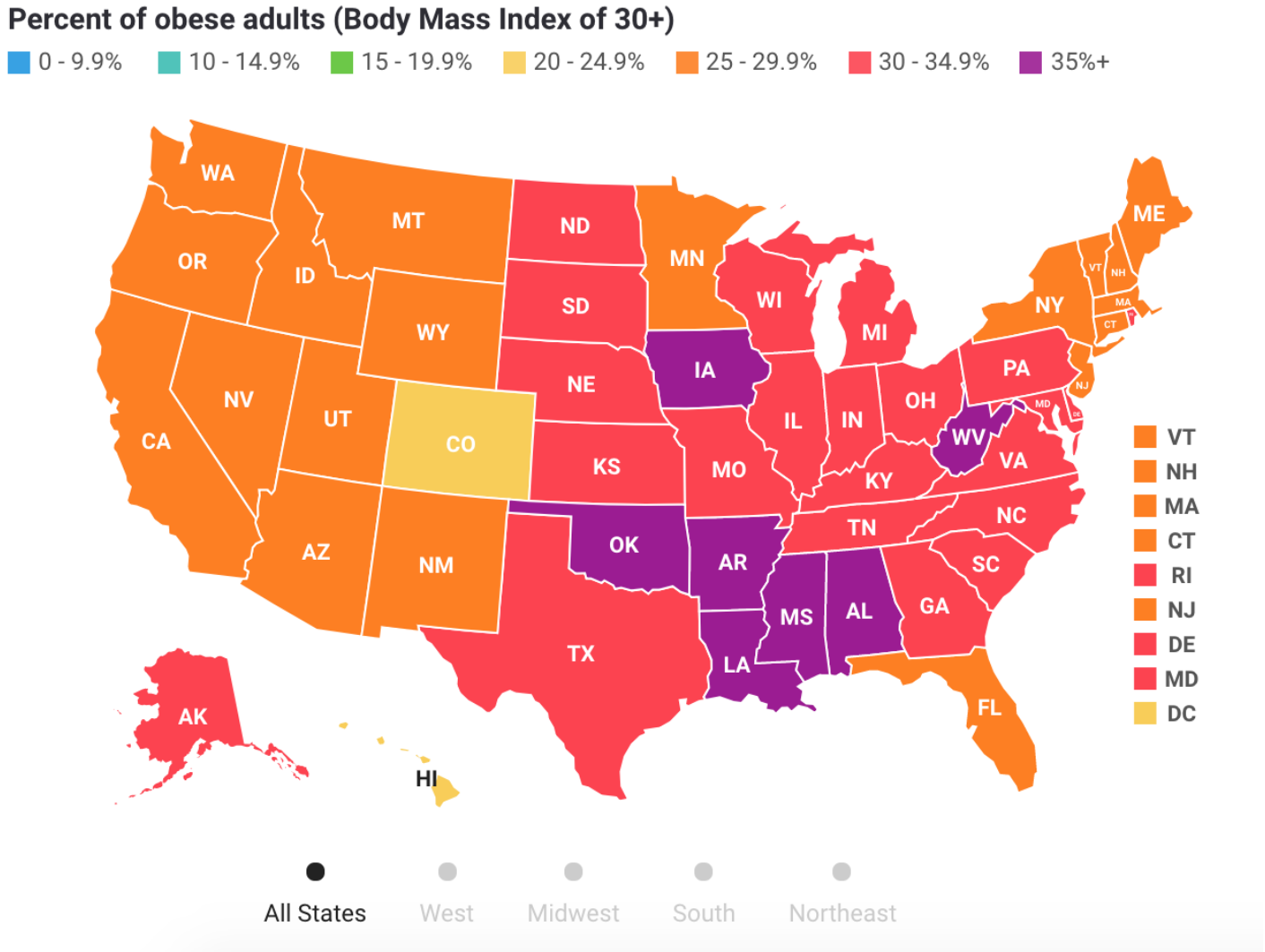
Adult Obesity in the United States 1990



BMI:
Normal 18.5-25
Overweight 25-30
Obese > 30
Severely obese >35

https://stateofobesity.org/adult-obesity/

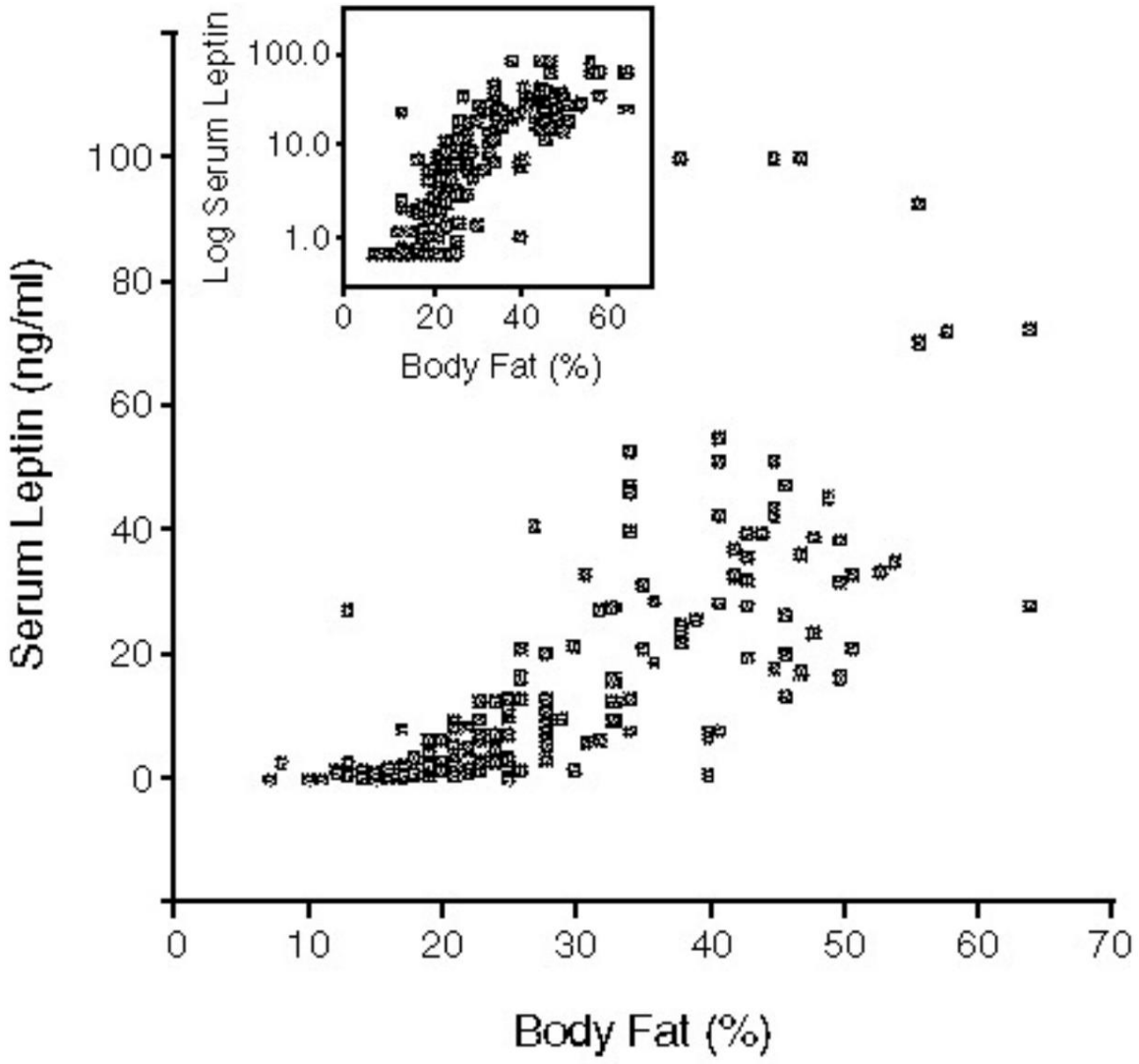
2017Adult Obesity in the United States



BMI:
Normal 18.5-25
Overweight 25-30
Obese > 30
Severely obese >35

https://stateofobesity.org/adult-obesity/

Blood Leptin concentration correlates with body weight



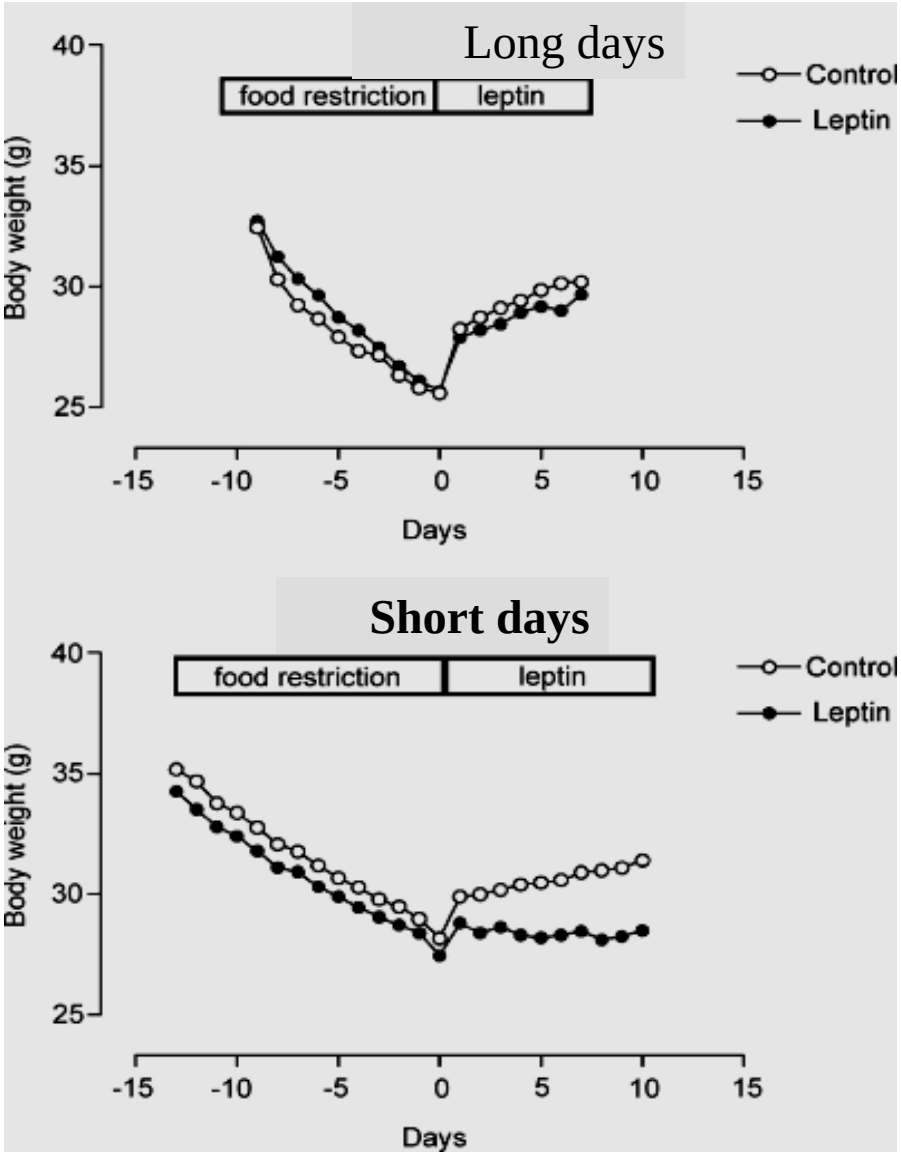
What can you conclude from this graph?

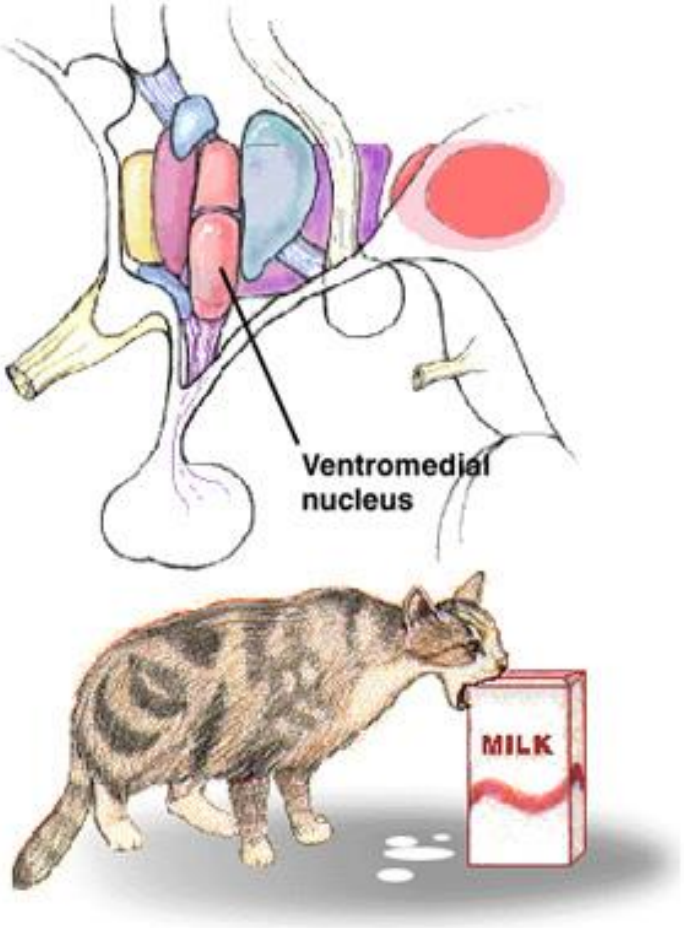
Potential contributors to leptin resistance in obesity

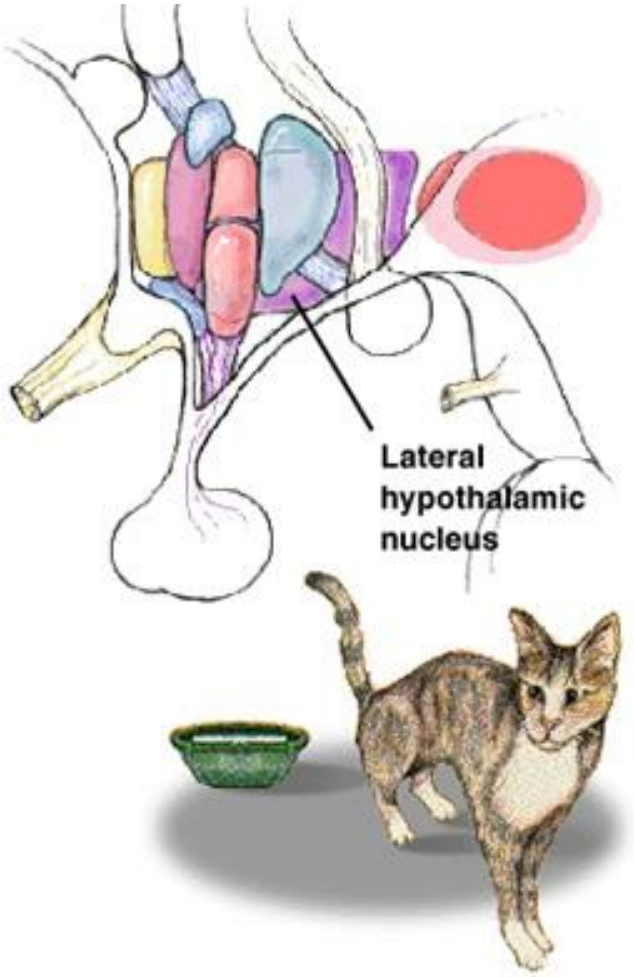
- **Deficient BBB crossing** – High levels of triglicerides is thought to inhibit transport of leptin through the BBB.
- **Hyperleptinemia** - Chronic exposure to high levels of circulating leptin causes leptin resistance, presumably by over-activating negative feedback regulators.
- **Inflammation** - Low-grade, chronic inflammation is closely associated with various metabolic disorders including obesity. High fat diet (HFD) feeding can promote inflammation in the hypothalamus.
- **Hypothalamic ER stress** - Observed in HFD-fed mice. Pharmacological ER stress inducers impair leptin signaling, whereas treatments with chemical ER chaperons relieve hypothalamic ER stress and decrease body weights in ob/ob mice.

Front Med. 2013 Jun; 7(2): 207–222.

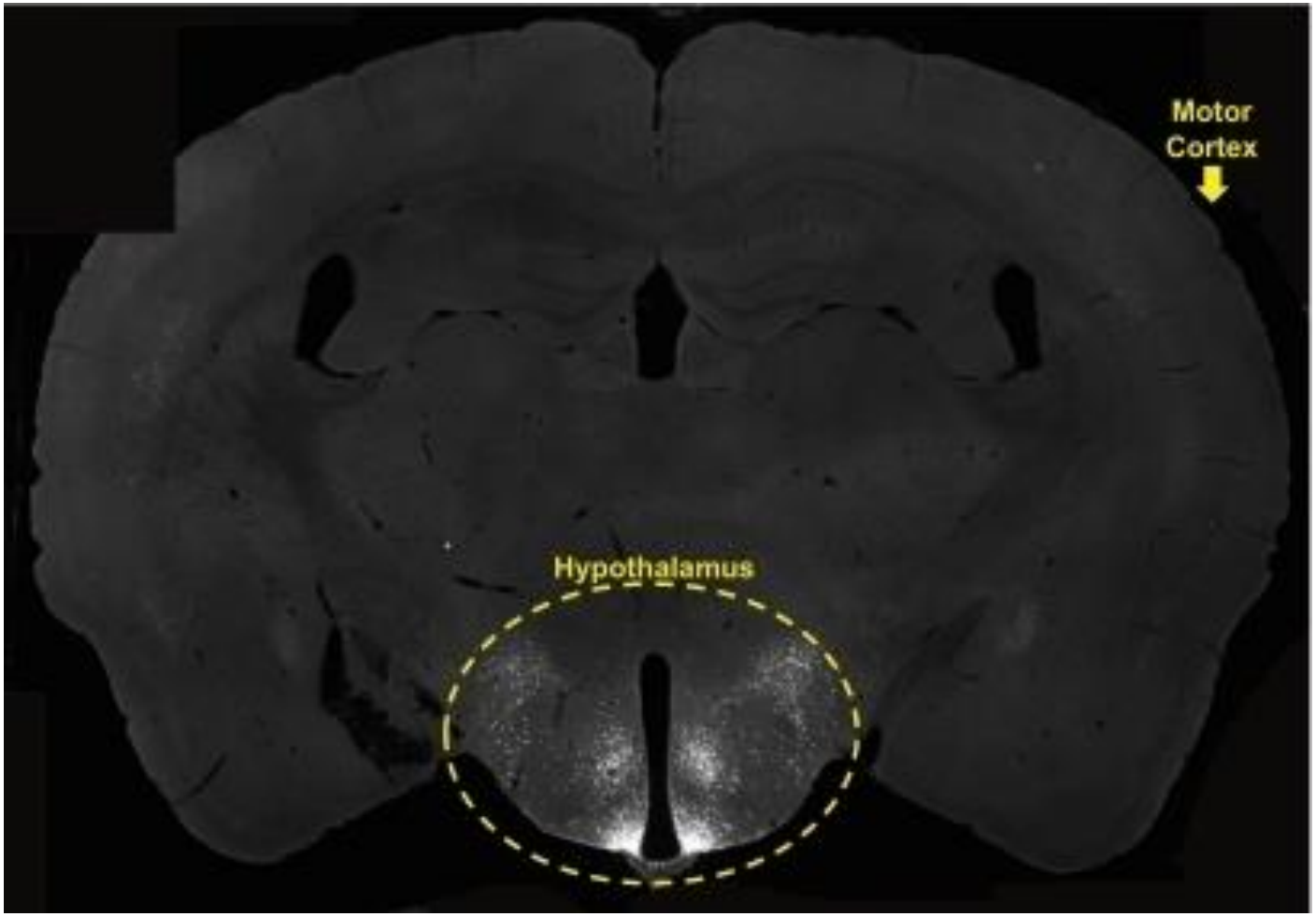
Leptin resistance in humbsters under long days



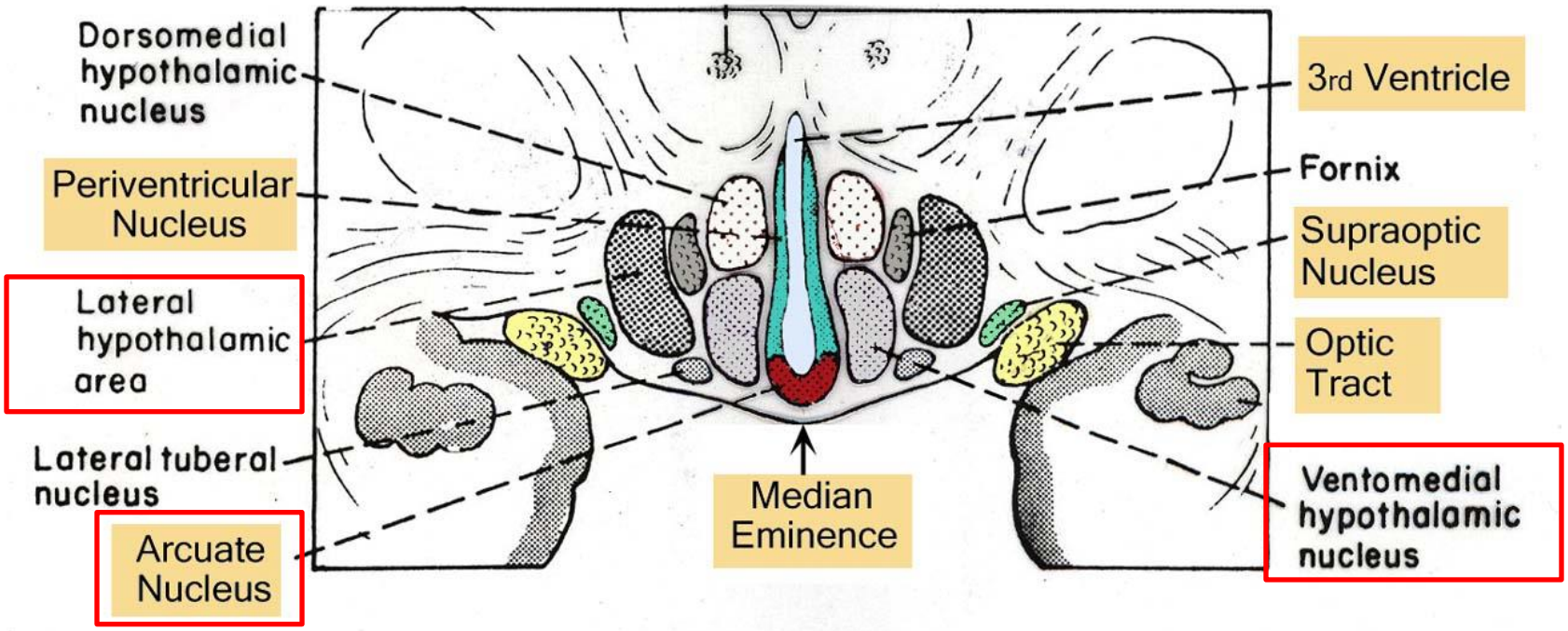

Ventromedial
nucleus
MILK


Lateral
hypothalamic
nucleus

Leptin receptor-expressing neurons in the arcuate nucleus of the hypothalamus



Hypothalamic Nuclei



What is happening in the hypothalamus?

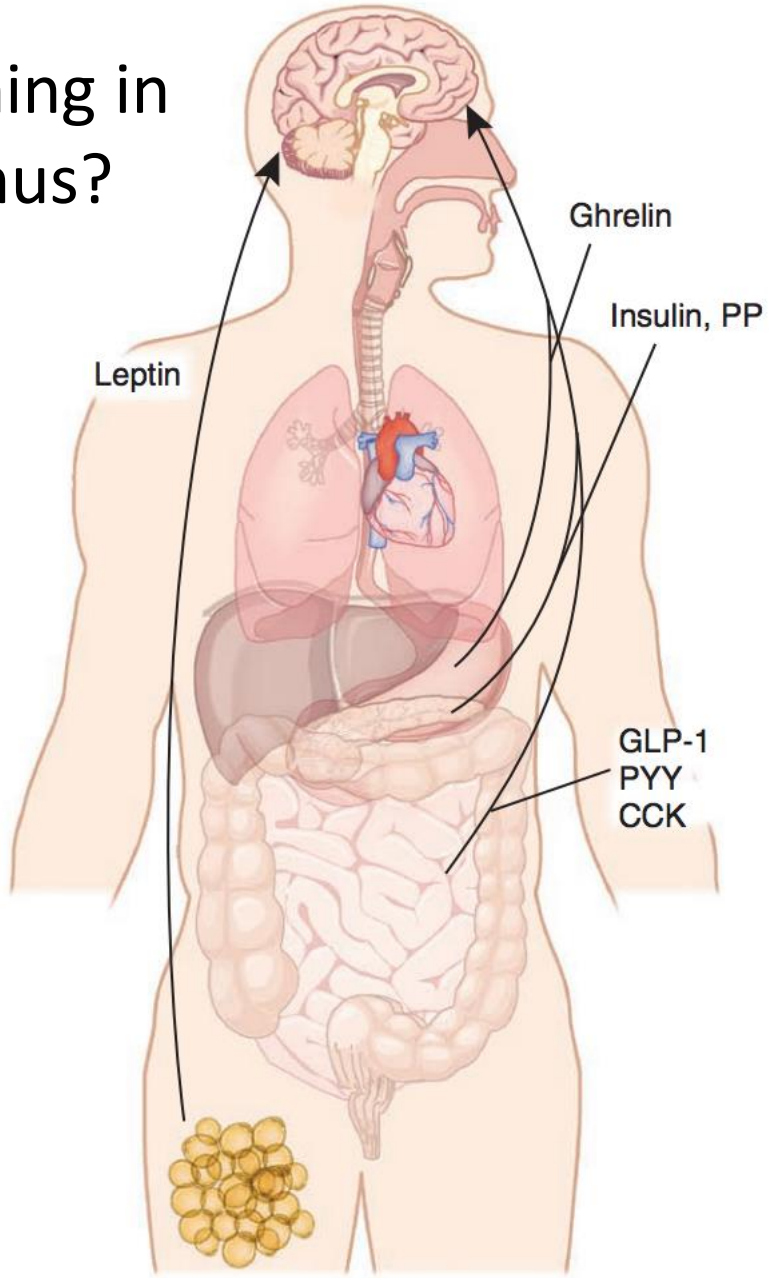
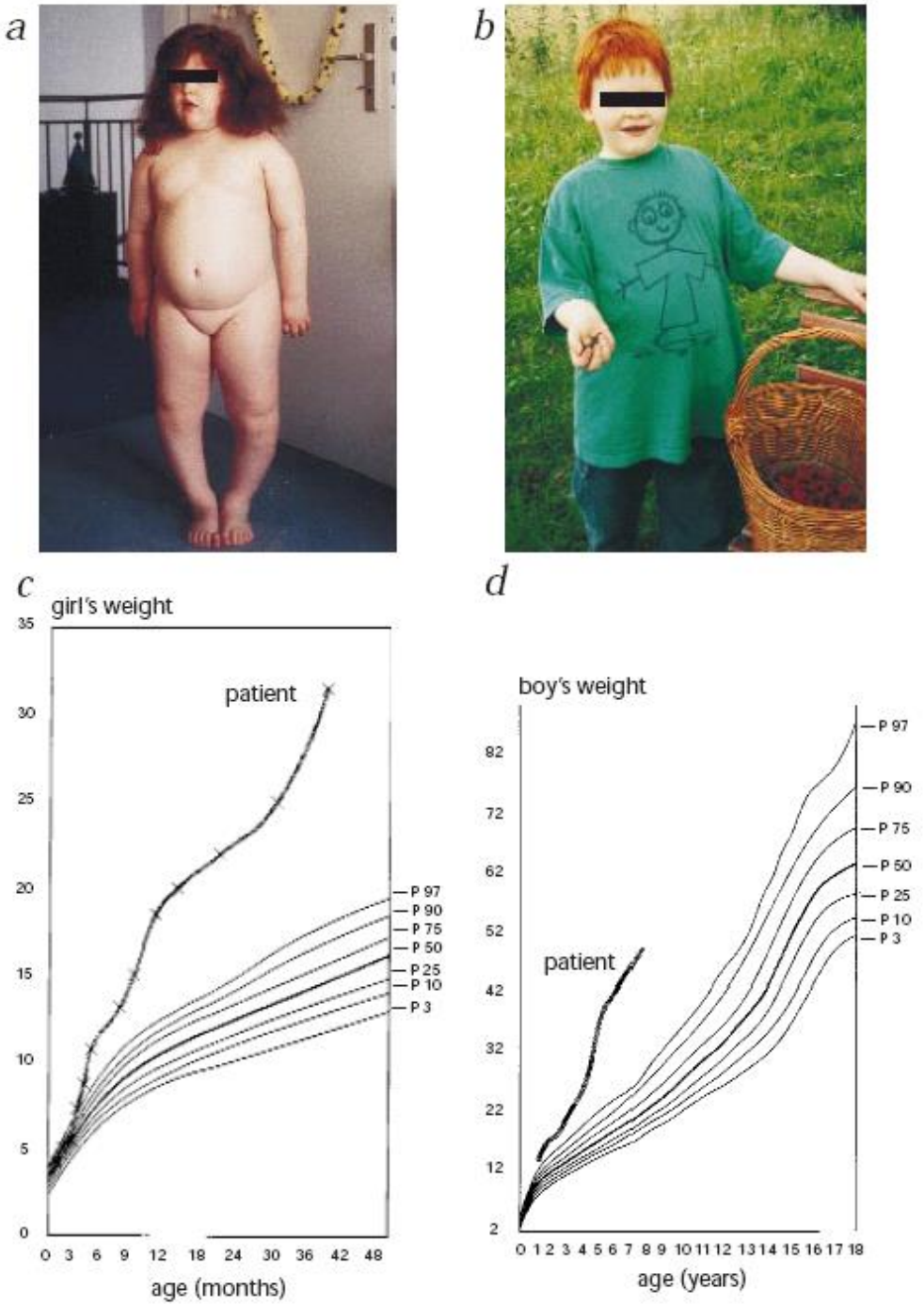
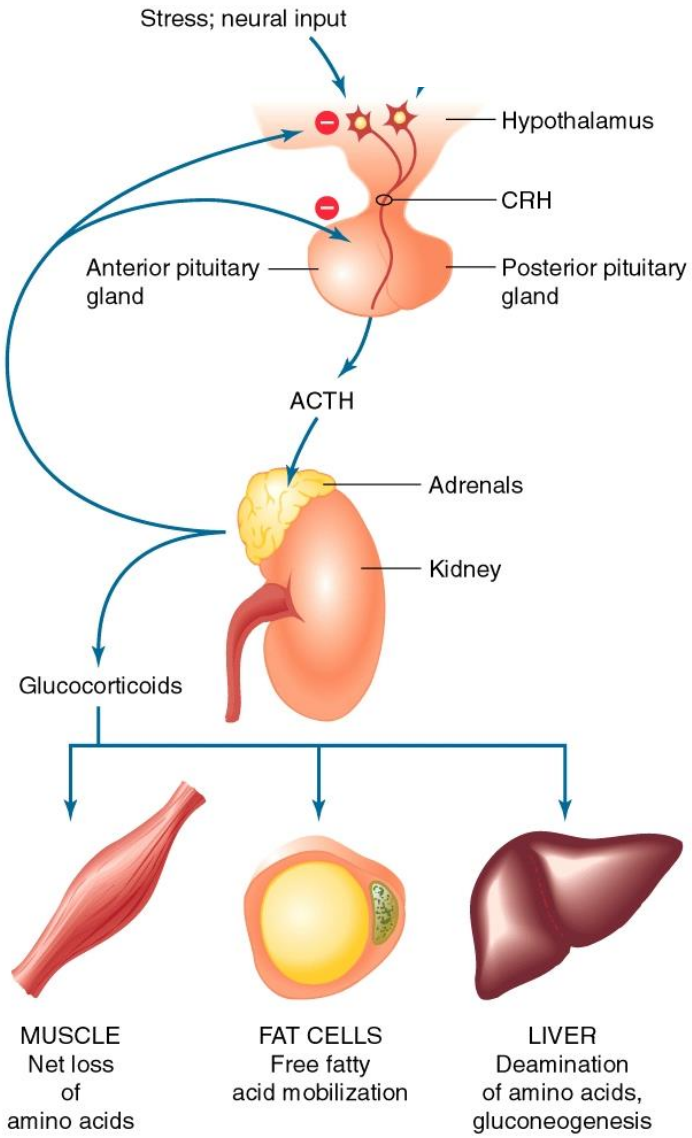


Figure 7–54. A neuroendocrine syndrome of adrenocorticotropic hormone insufficiency, obesity, and red hair resulting from a null mutation in the pro-opiomelanocortin gene. (Photo kindly provided by Dr. A. Gruters, Berlin.)



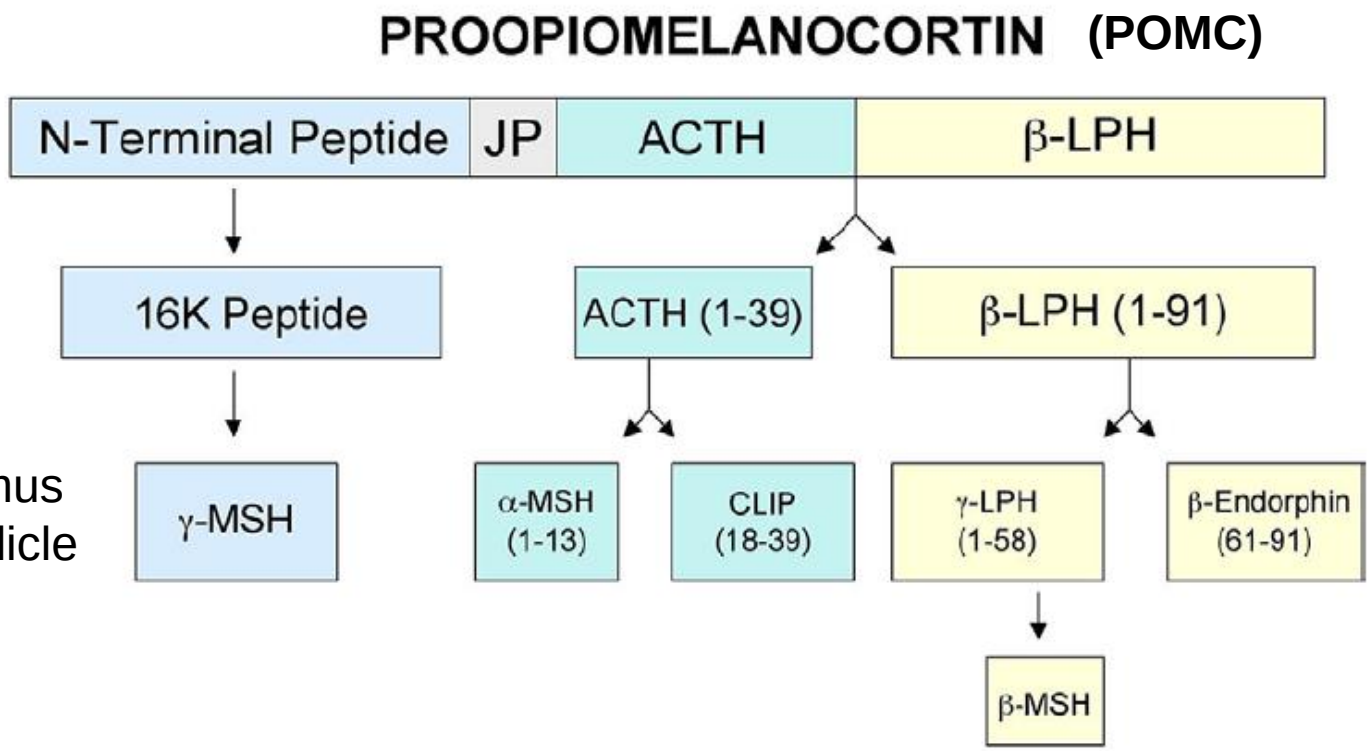
Krude et al., 1998



CRH – corticotropin releasing hormone

ACTH – corticotropin; adrenocorticortrophic hormone

Glucocorticoids, cortisol or corticosterone

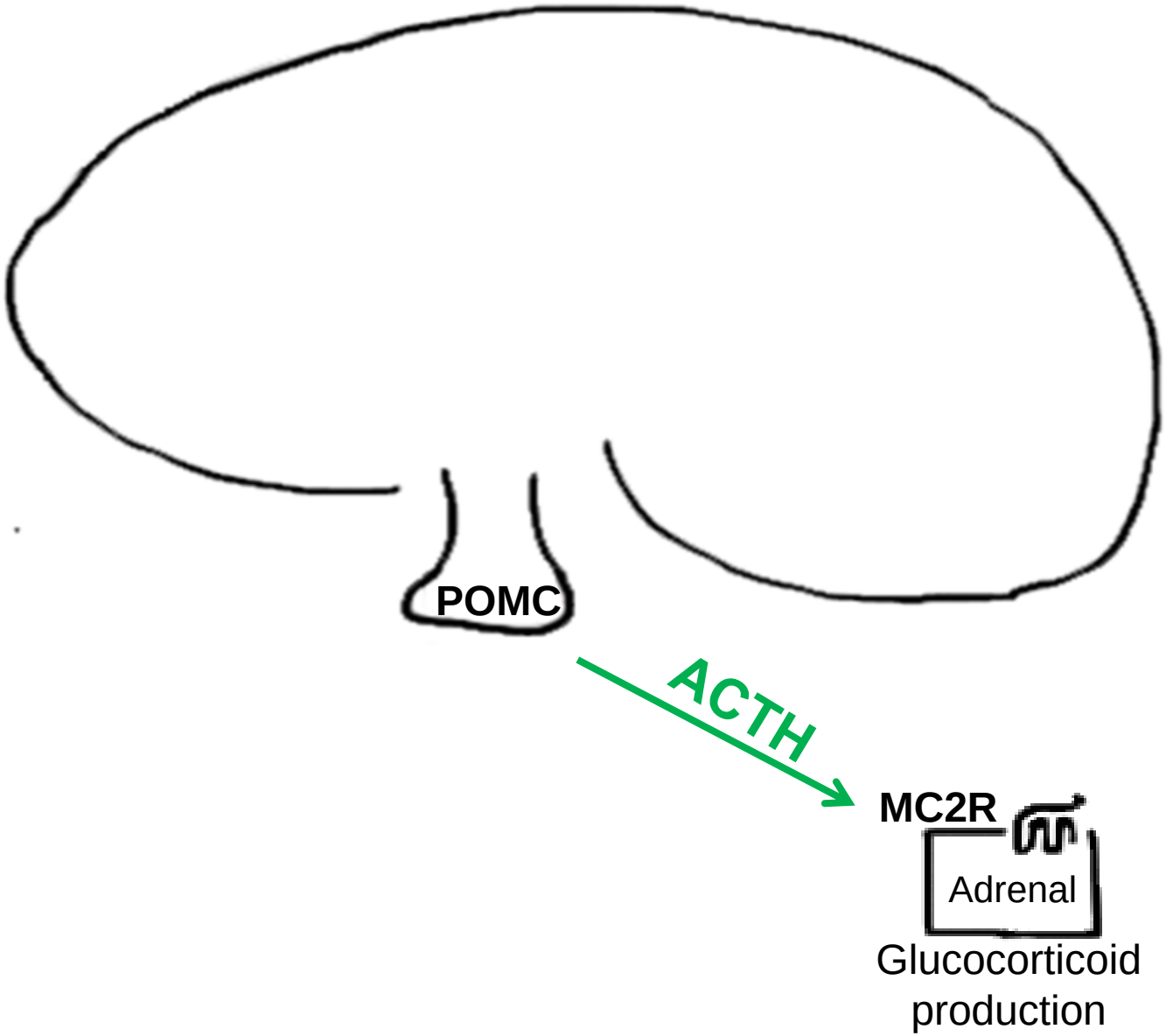


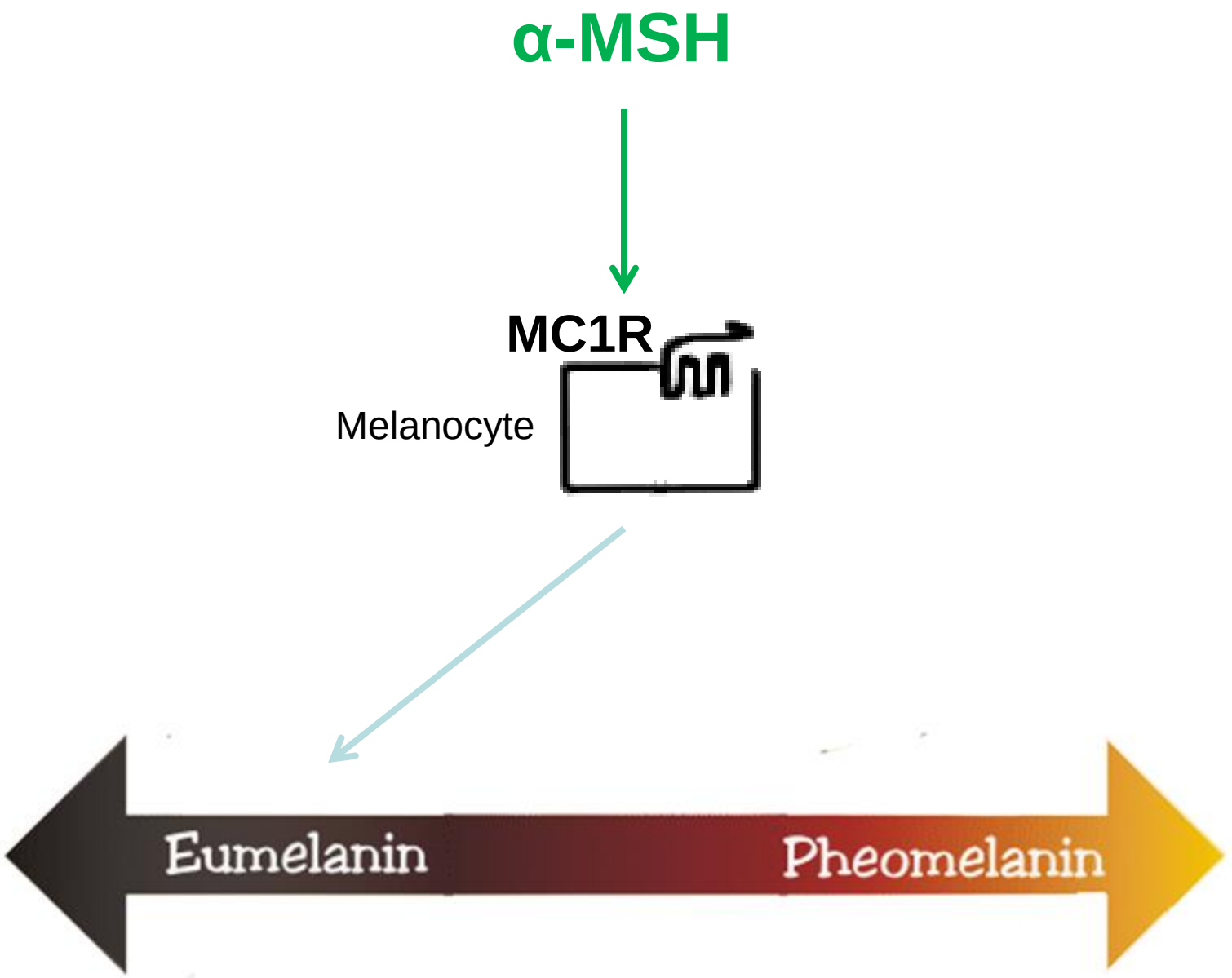
Pituitary

Hypothalamus and hair follicle

Figure 2. Schematic diagram of the POMC precursor molecule and the major peptide products which are derived from this precursor by endoproteolytic cleavage. (JP = Joining peptide; LPH= Lipotropin; CLIP= corticotropin-like-intermediate lobe peptide).

POMC functions in the stress response




α-MSH
MC1R
Melanocyte
Eumelanin
Pheomelanin

α-MSH

MC1R

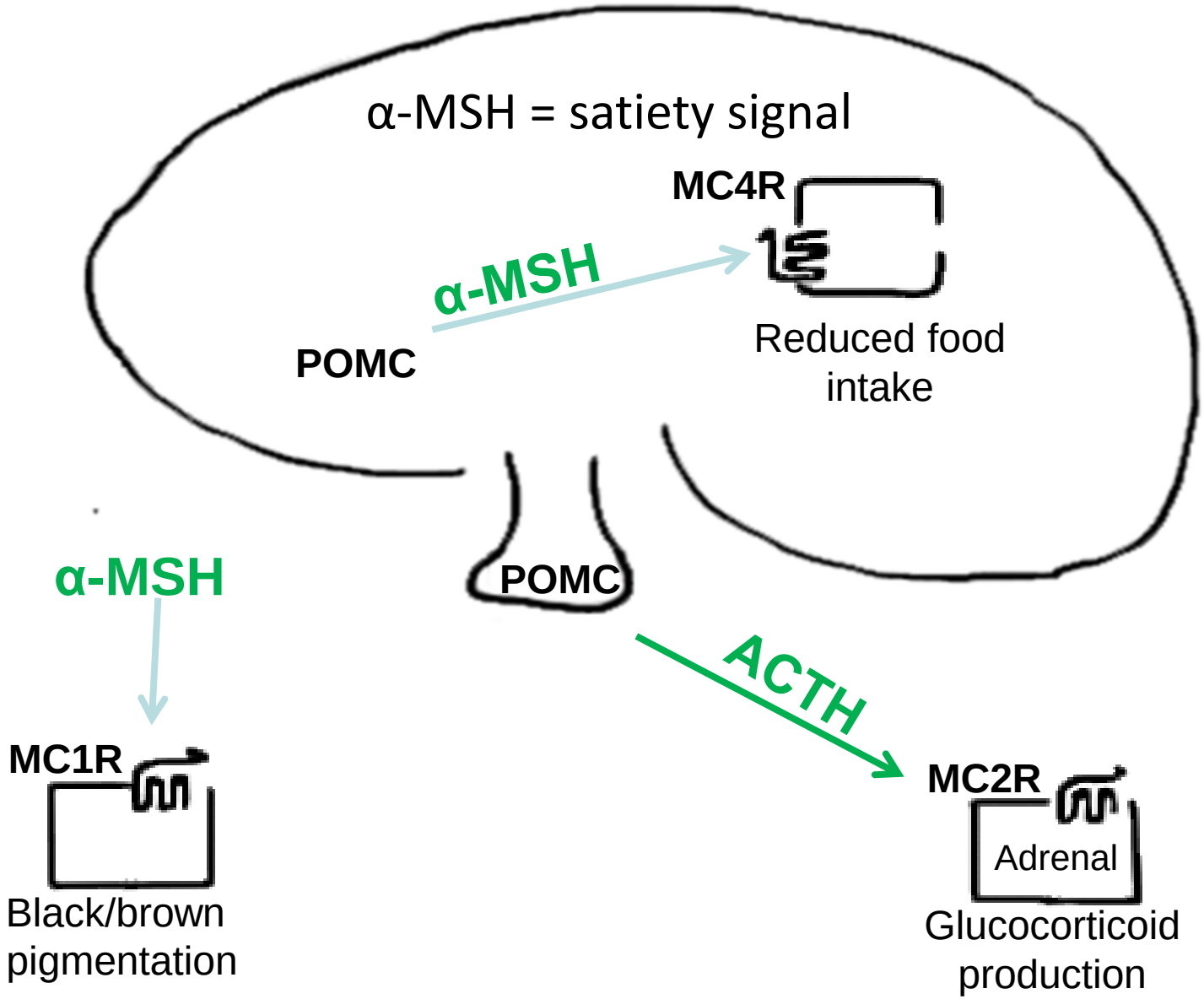
Melanocyte

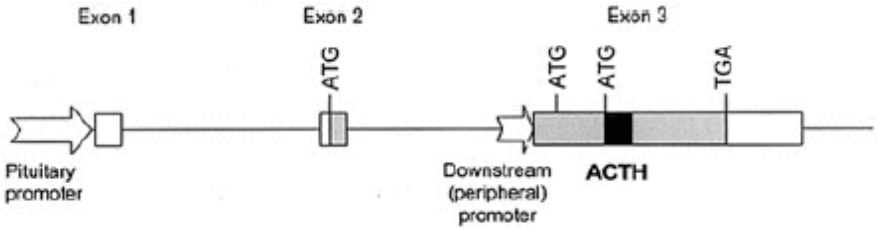
Red pigmentation

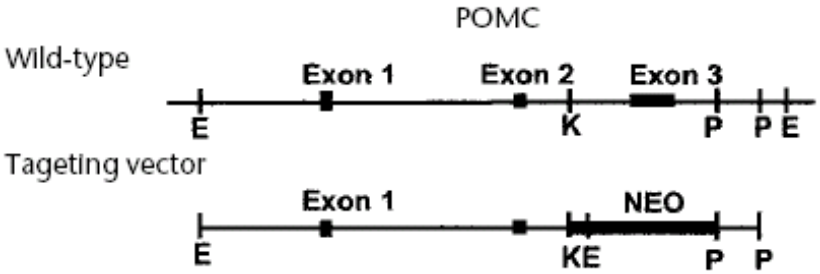
Eumelanin

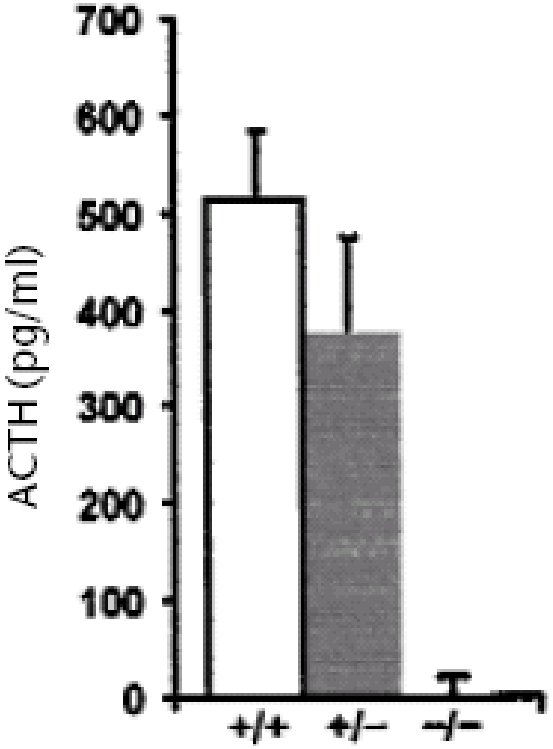
Pheomelanin

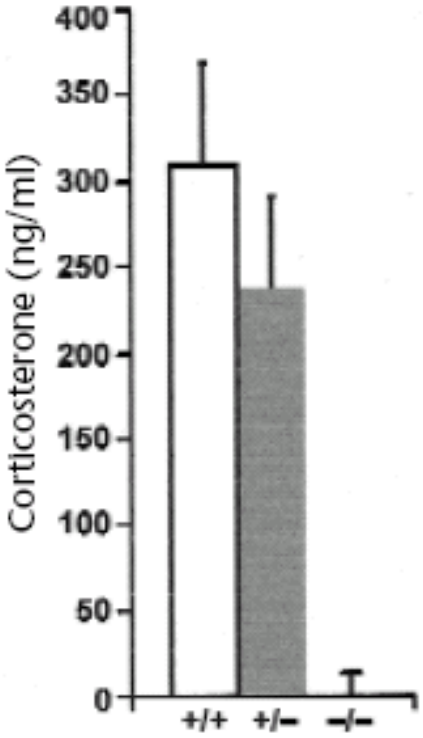
POMC functions in stress response, pigmentation and food consumption









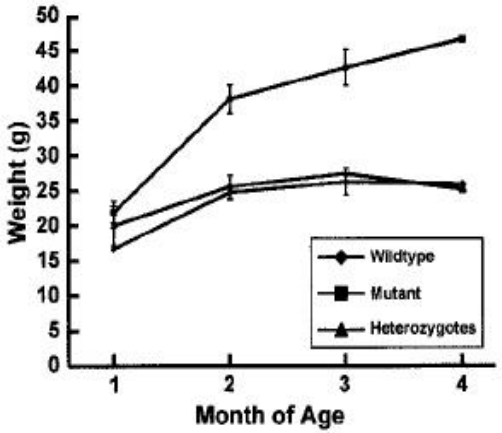


Yaswen et al., 1999

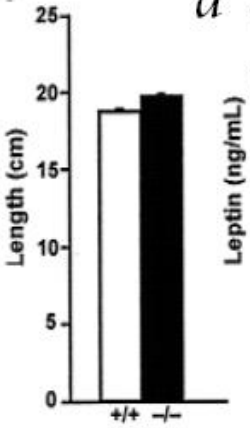
a

–/– +/+

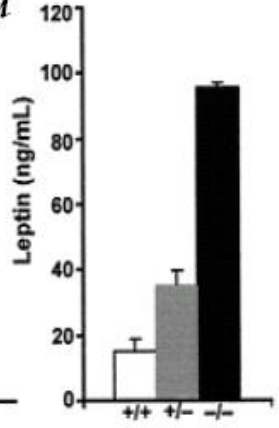
b



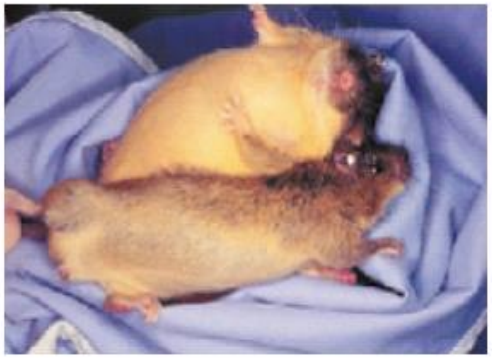
c



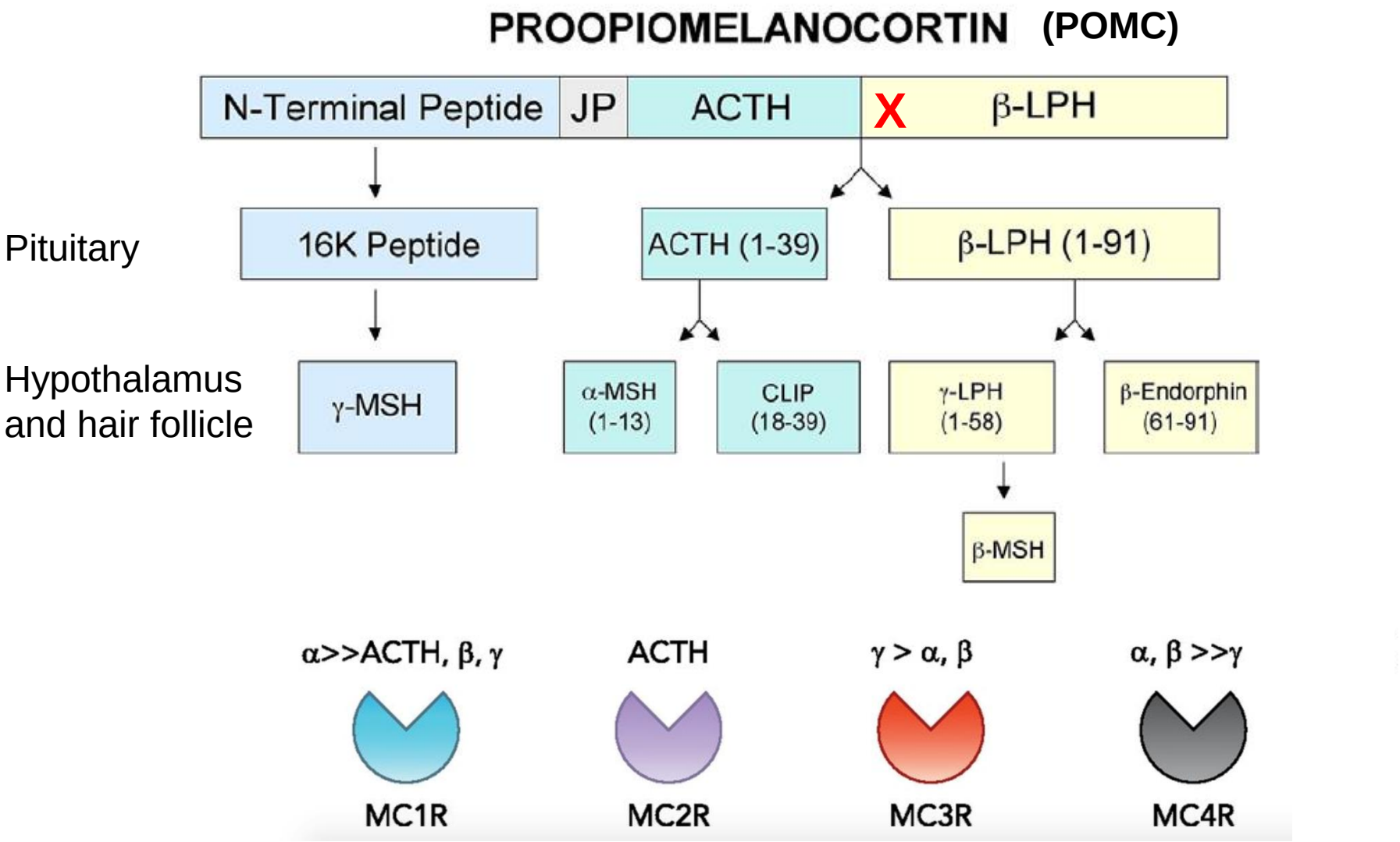
d



g

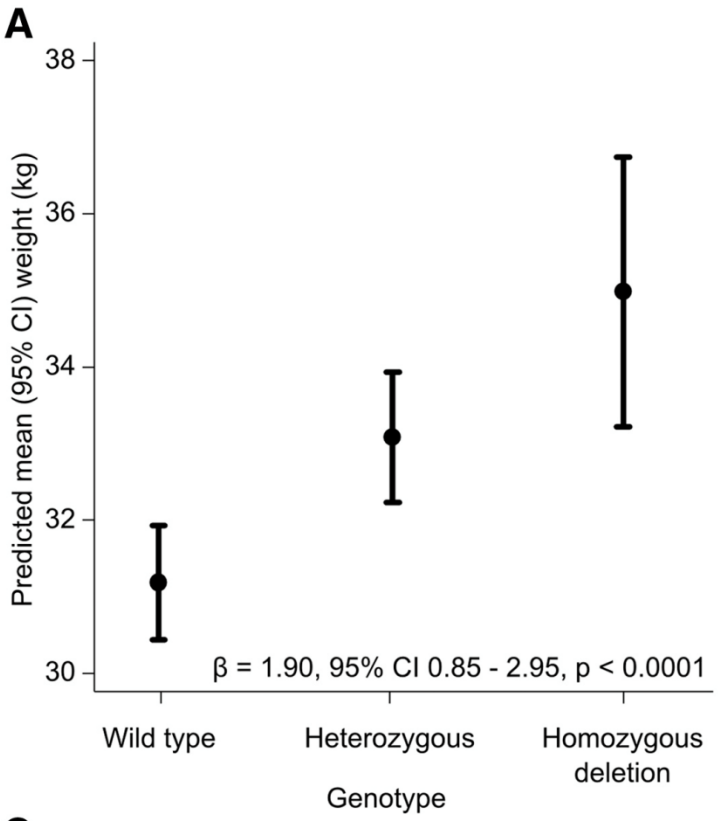


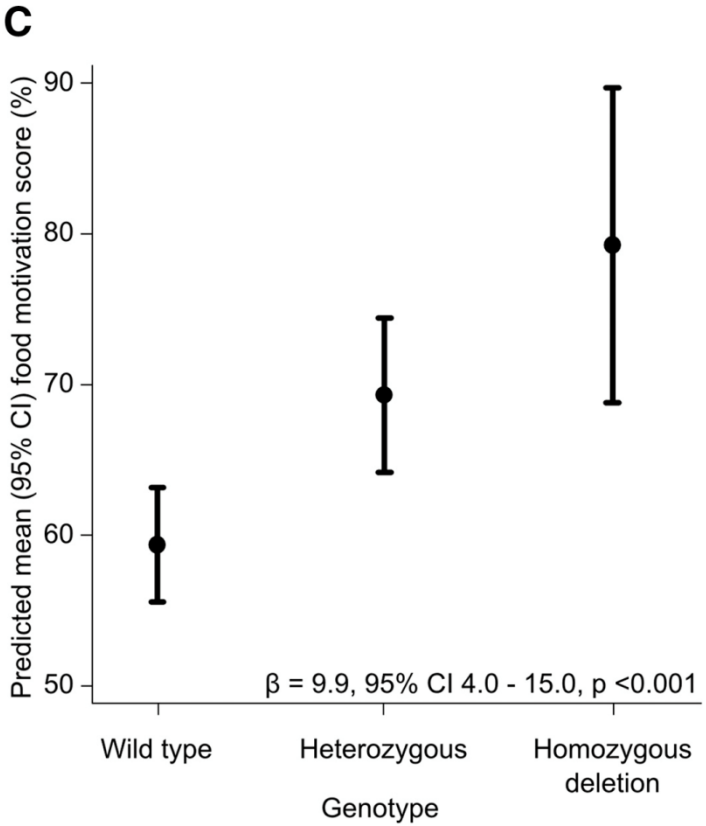
Yaswen et al., 1999


PROOPIOMELANOCORTIN (POMC)
N-Terminal Peptide
JP
ACTH
X
β-LPH
16K Peptide
ACTH (1-39)
β-LPH (1-91)
γ-MSH
α-MSH (1-13)
CLIP (18-39)
γ-LPH (1-58)
β-Endorphin (61-91)
β-MSH
Pituitary
Hypothalamus and hair follicle
α>>ACTH, β, γ
ACTH
γ > α, β
α, β >>γ
MC1R
MC2R
MC3R
MC4R

A Deletion in the Canine *POMC* Gene Is Associated with Weight and Appetite in Obesity-Prone Labrador Retriever Dogs

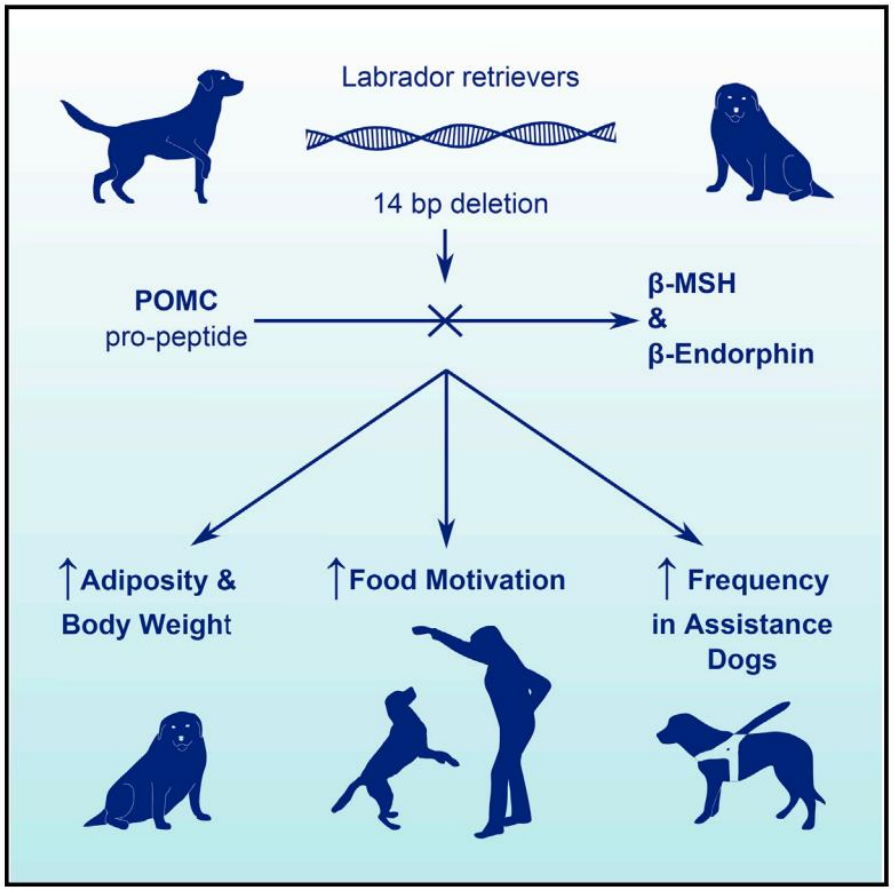
Eleanor Raffan[14], Rowena J. Dennis, Conor J. O'Donovan, Julia M. Becker, Robert A. Scott, Stephen P. Smith, David J. Withers, Claire J. Wood, Elena Conci, Dylan N. Clements, Kim M. Summers, Alexander J. German, Cathryn S. Mellersh, Maja L. Arendt, Valentine P. Iyemere, Elaine Withers, Josefin Söder, Sara Wernersson, Göran Andersson, Kerstin Lindblad-Toh, Giles S.H. Yeo[13], Stephen O'Rahilly[13],





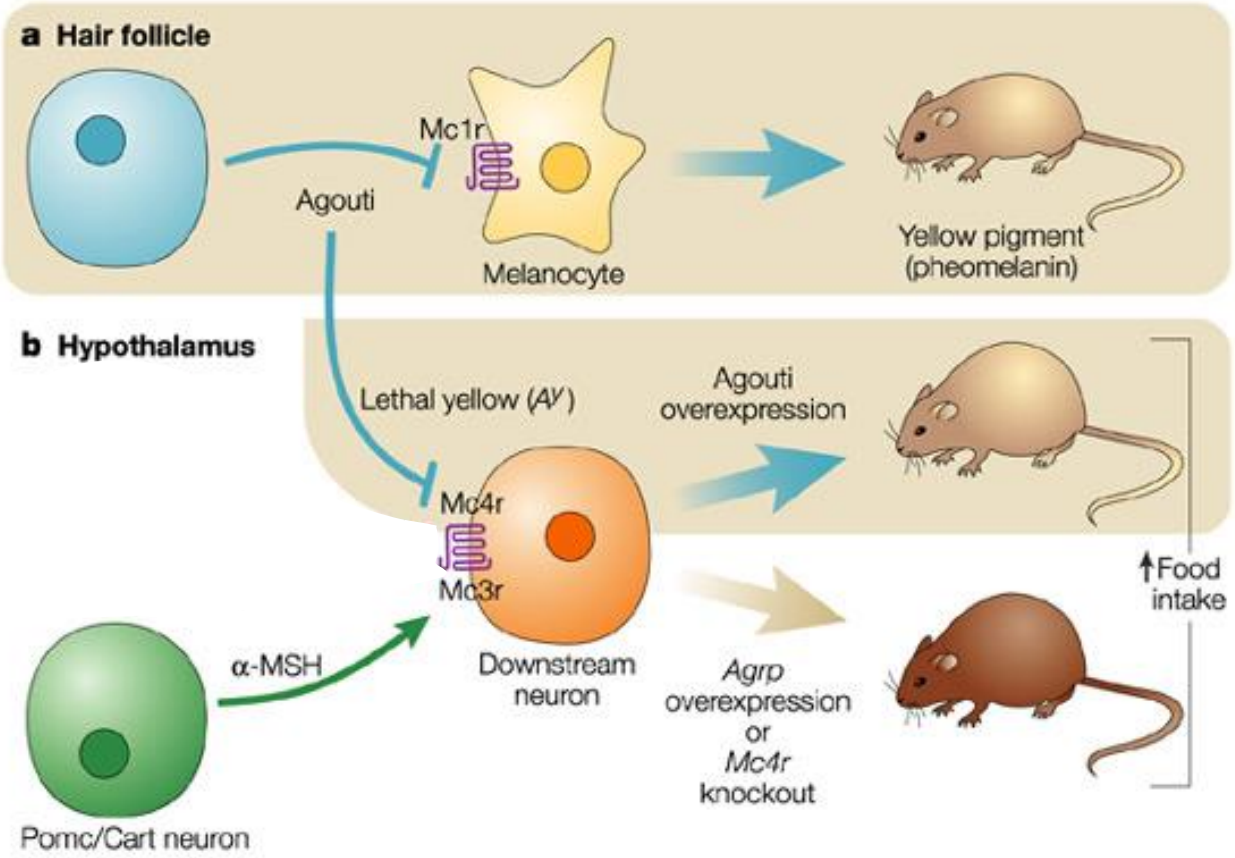
A Deletion in the Canine *POMC* Gene Is Associated with Weight and Appetite in Obesity-Prone Labrador Retriever Dogs

Eleanor Raffan[14], Rowena J. Dennis, Conor J. O'Donovan, Julia M. Becker, Robert A. Scott, Stephen P. Smith, David J. Withers, Claire J. Wood, Elena Conci, Dylan N. Clements, Kim M. Summers, Alexander J. German, Cathryn S. Mellersh, Maja L. Arendt, Valentine P. Iyemere, Elaine Withers, Josefin Söder, Sara Wernersson, Göran Andersson, Kerstin Lindblad-Toh, Giles S.H. Yeo[13], Stephen O'Rahilly[13],

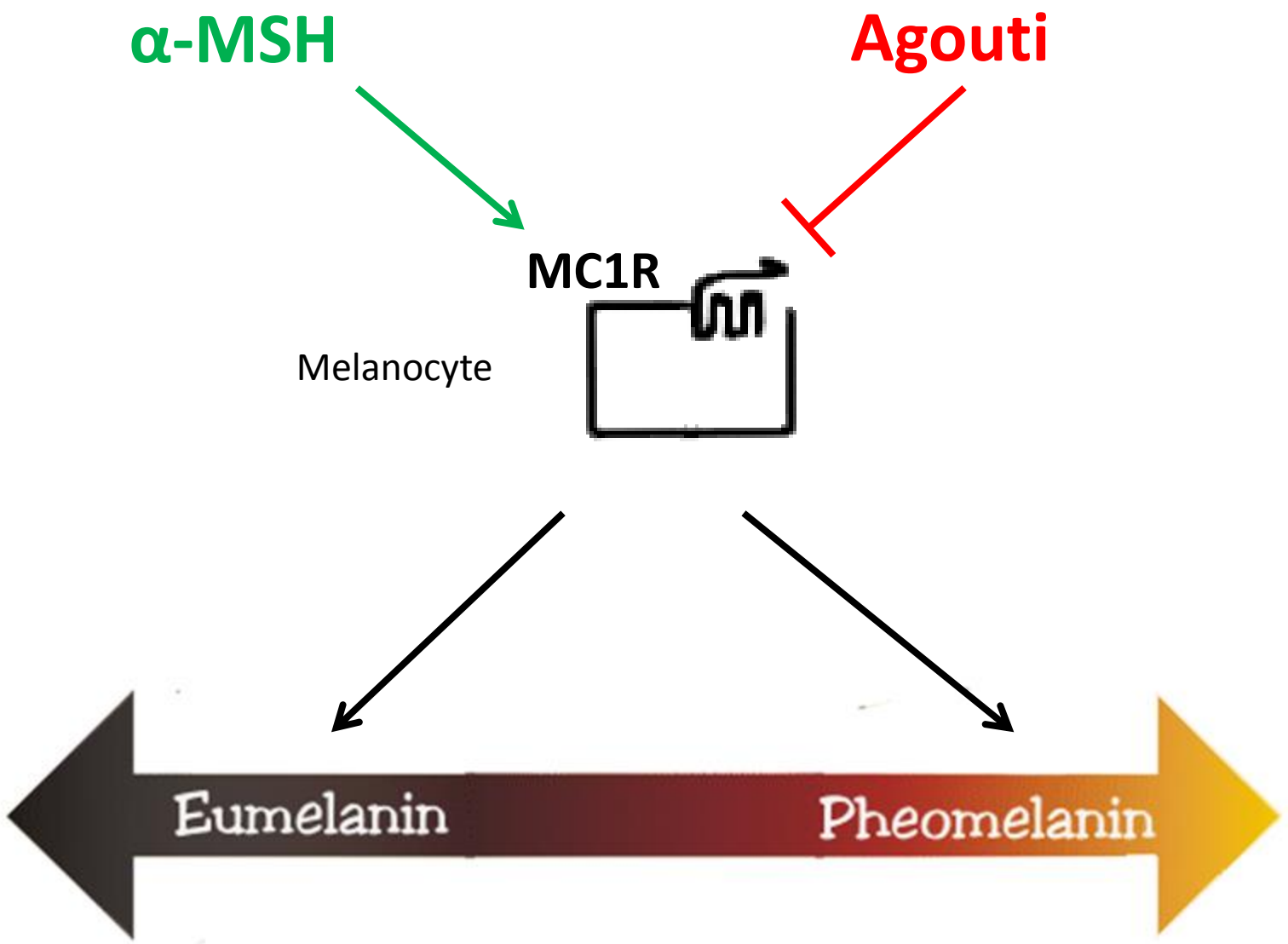


http://www.cam.ac.uk/research/news/genetic-variant-may-help-explain-why-labradors-are-prone-to-obesity

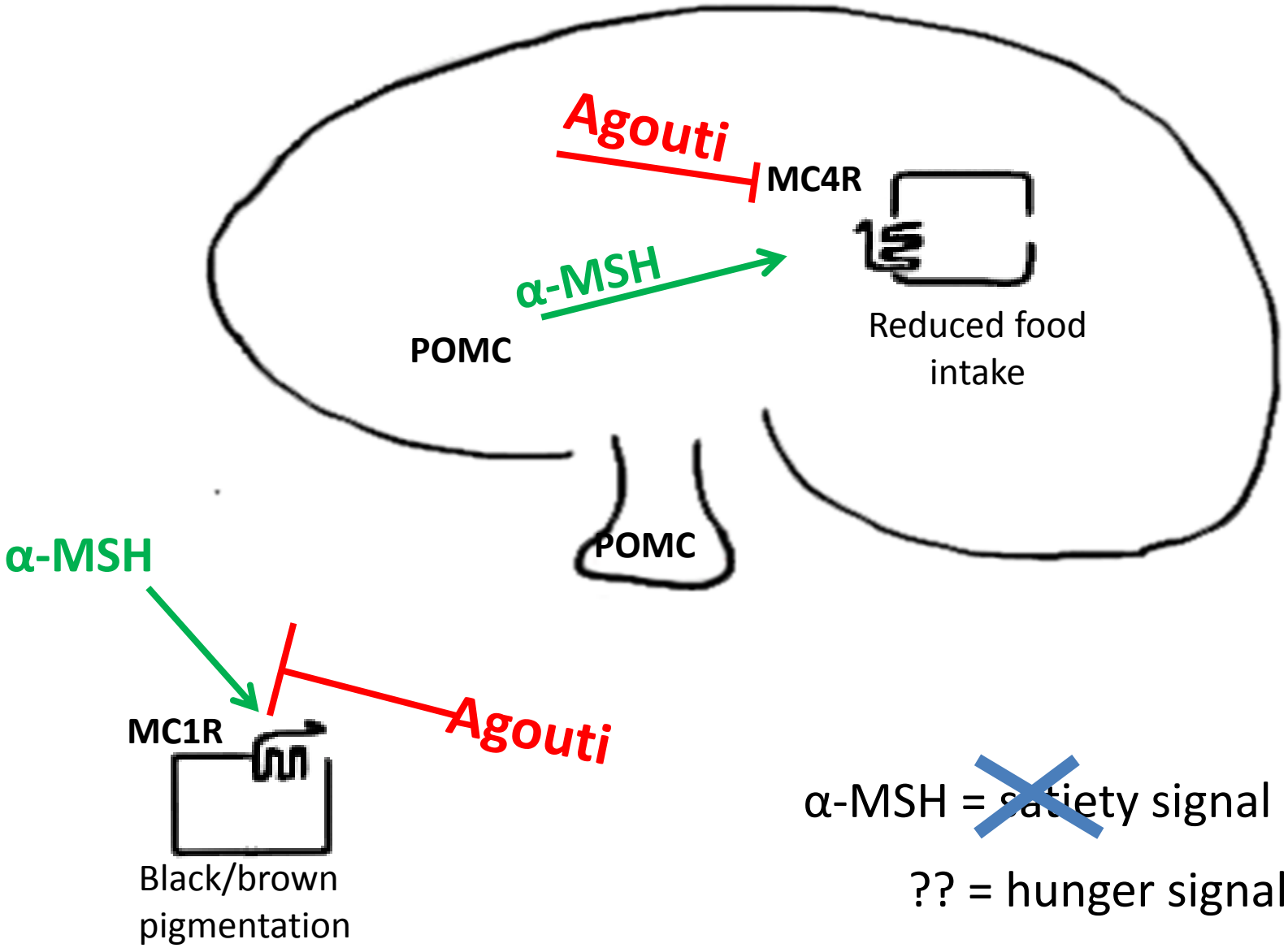
A^y mutation



Nature Reviews | Genetics

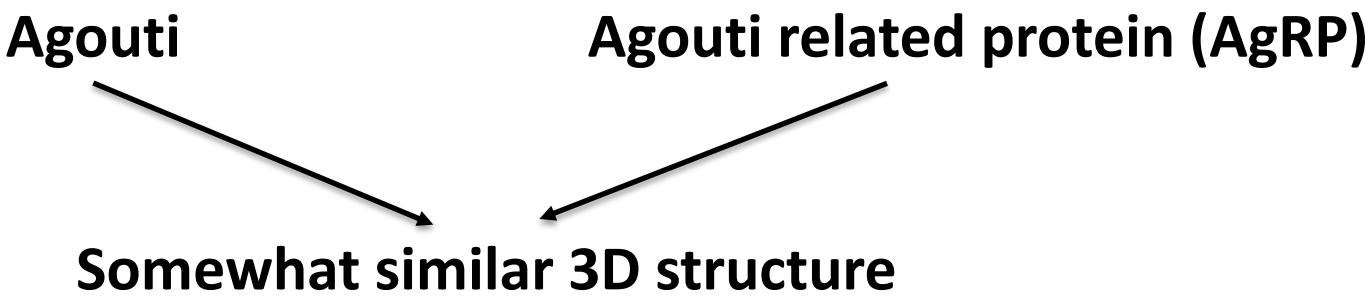

α-MSH
Agouti
MC1R
Melanocyte
Eumelanin
Pheomelanin

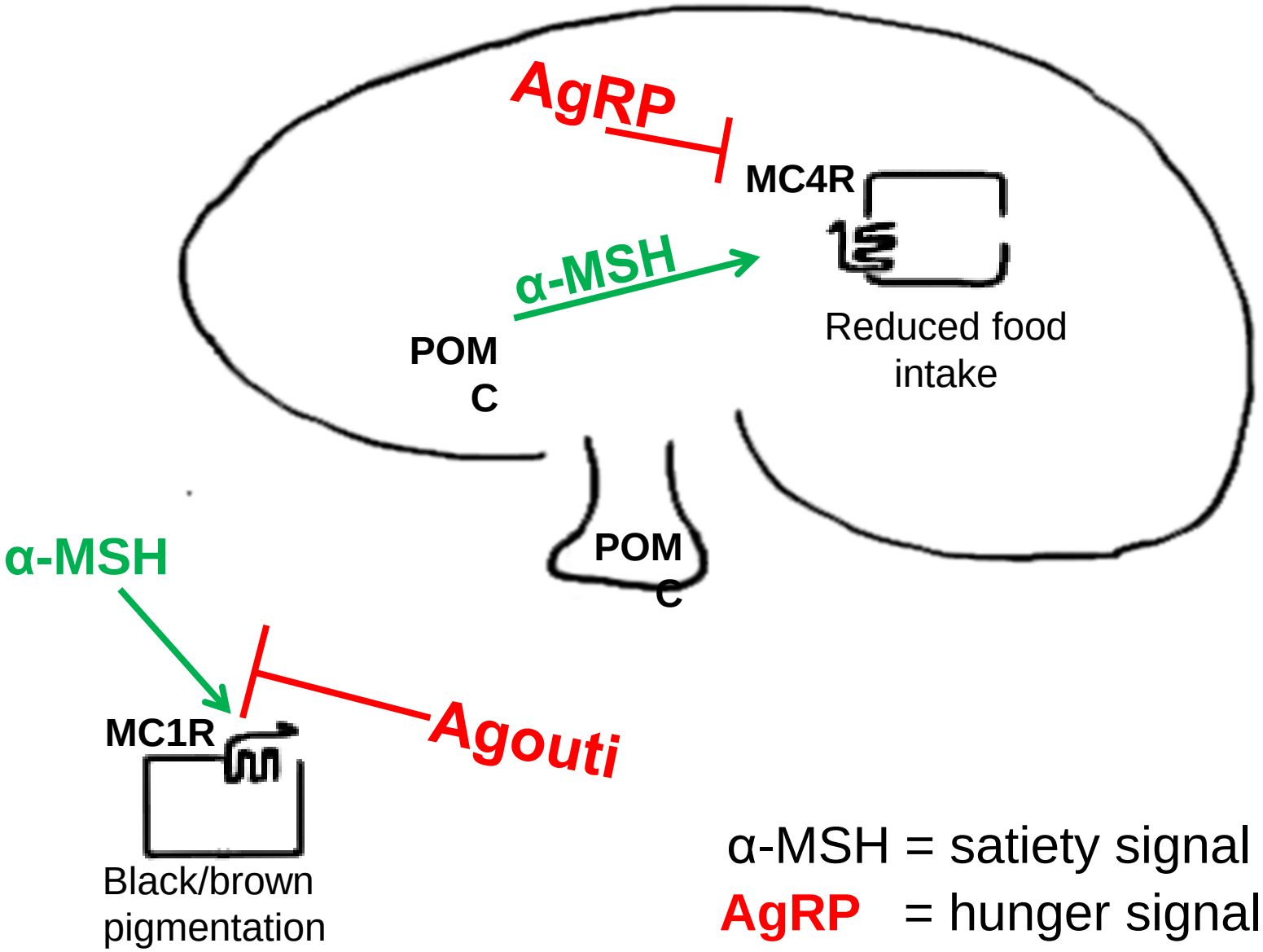
Ectopic overexpression of the agouti gene (A^y mutation)



α-MSH = ~~satiety~~ signal

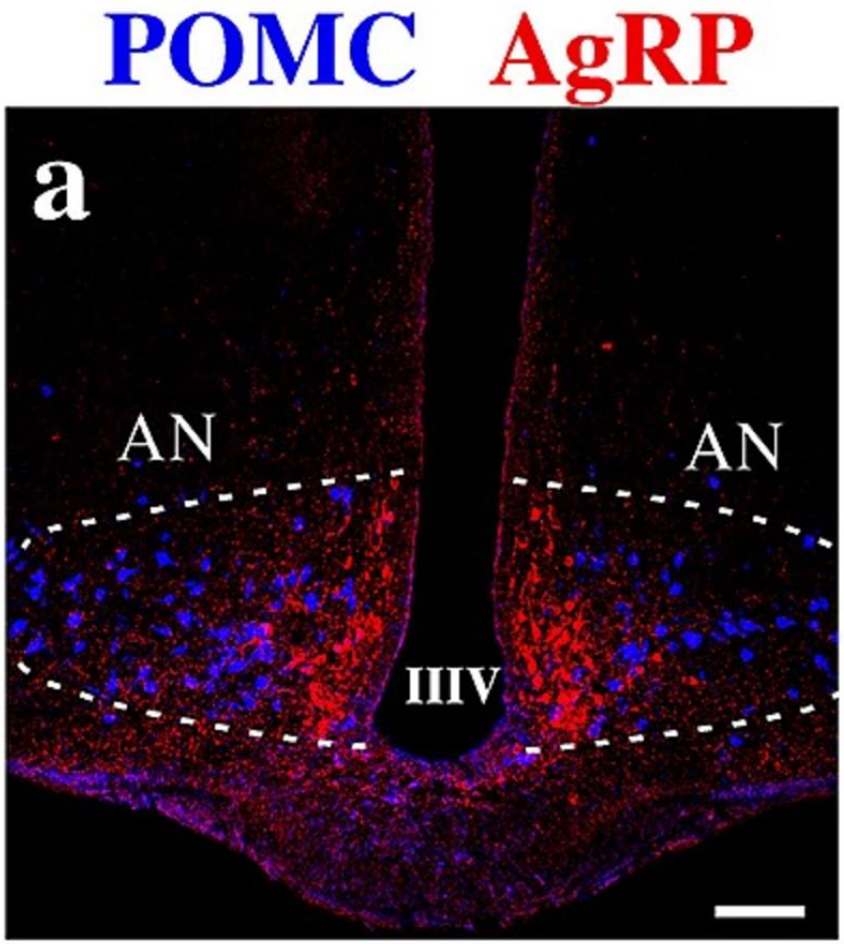
?? = hunger signal


Agouti
Agouti related protein (AgRP)
Somewhat similar 3D structure



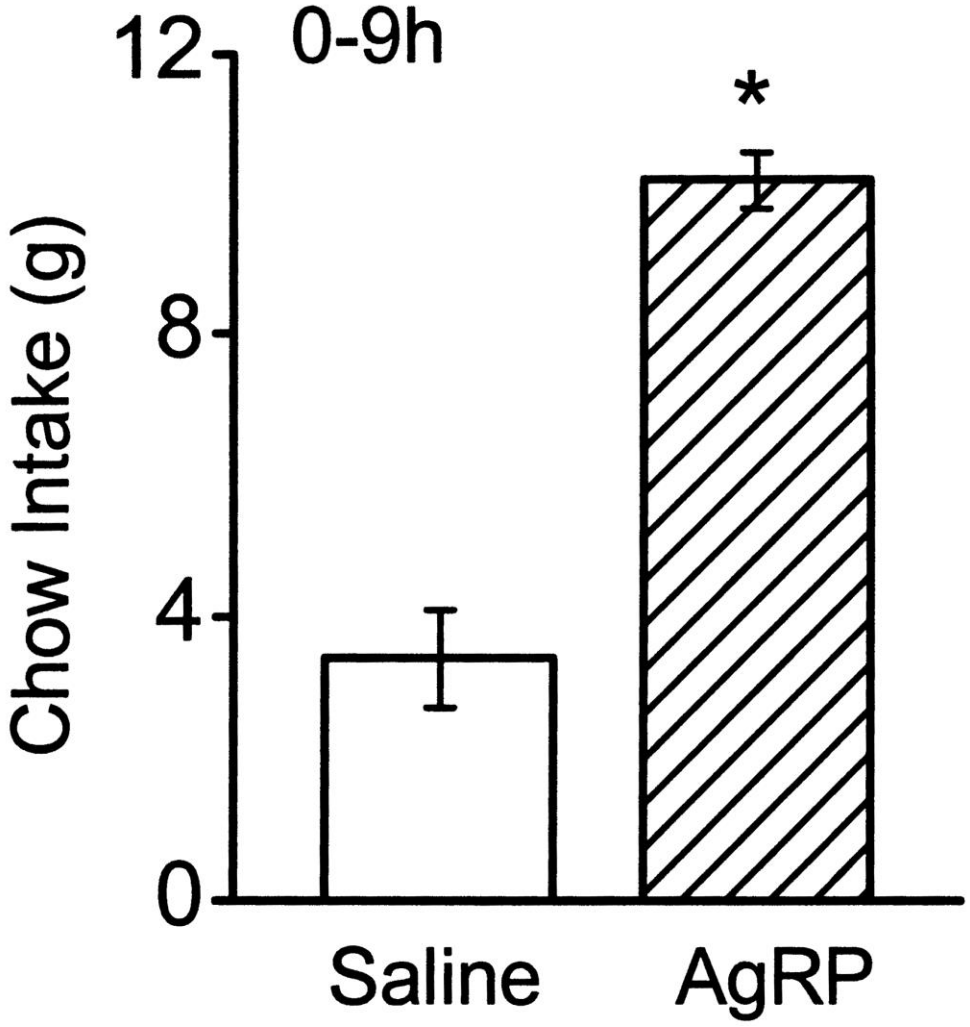
α-MSH = satiety signal

AgRP = hunger signal



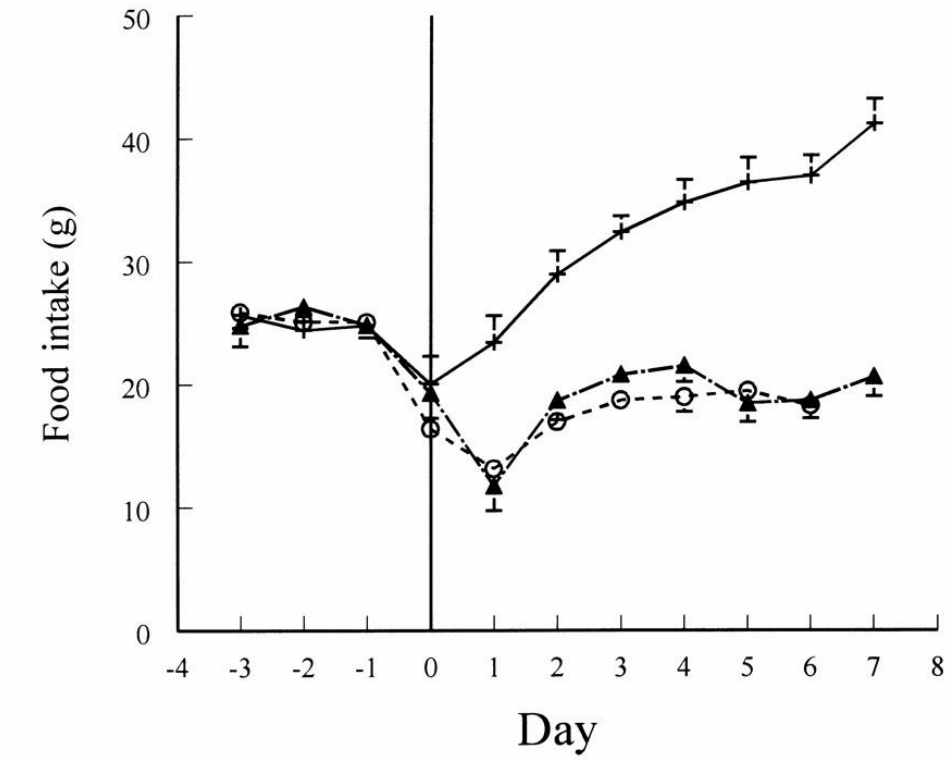
Both AgRP and POMC are localized in the arcuate nucleus (AN) of the hypothalamus.

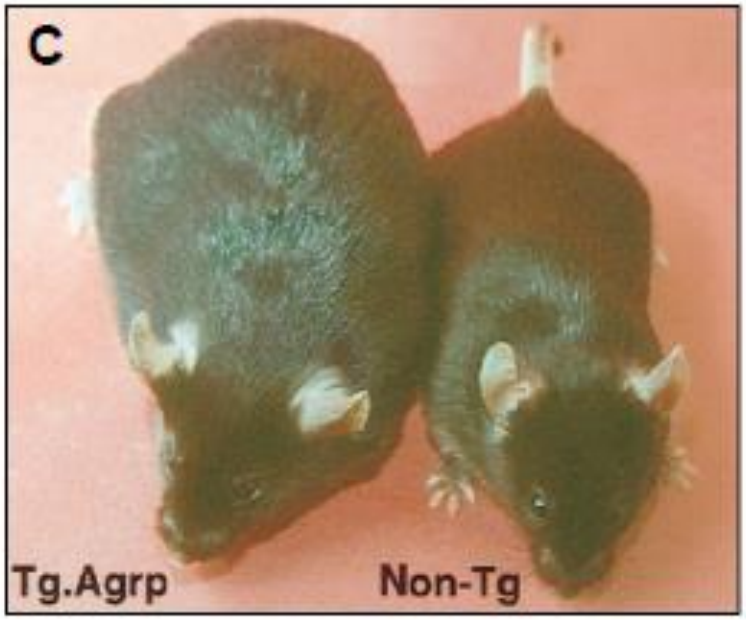
AgRP increases food intake

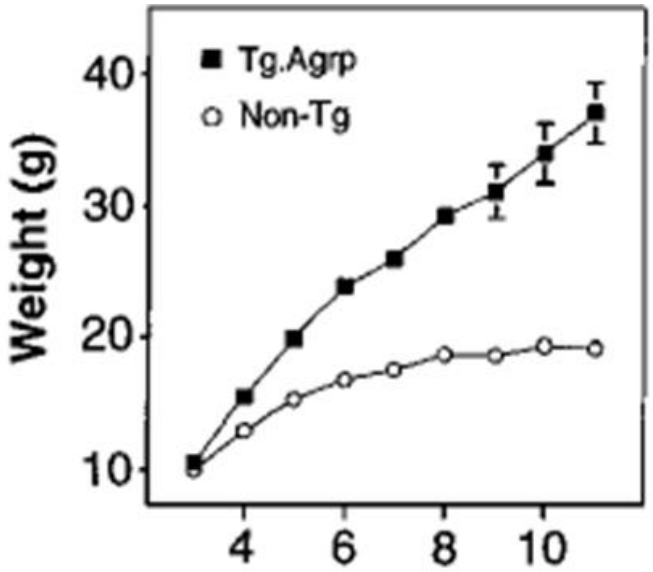


Zheng H et al. Am J Physiol Regul Integr Comp Physiol 2002;282:R1773-R1781

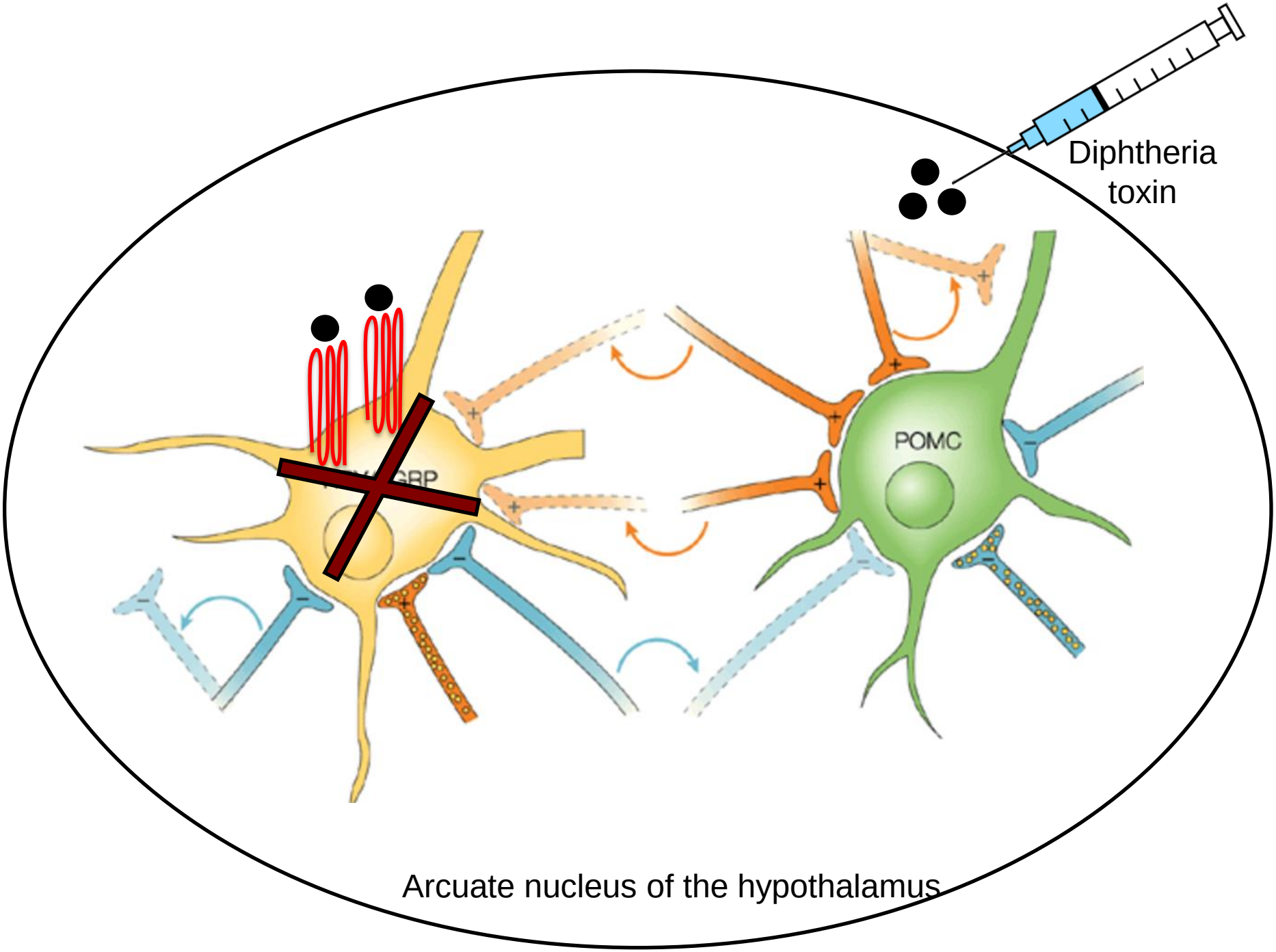
Daily food intake after chronic administration of 1 nmol/day AgRP (83-132) for 7 days.
+, AGRP ad libitum fed group
▲, saline control group.
○, AGRP pair-fed group

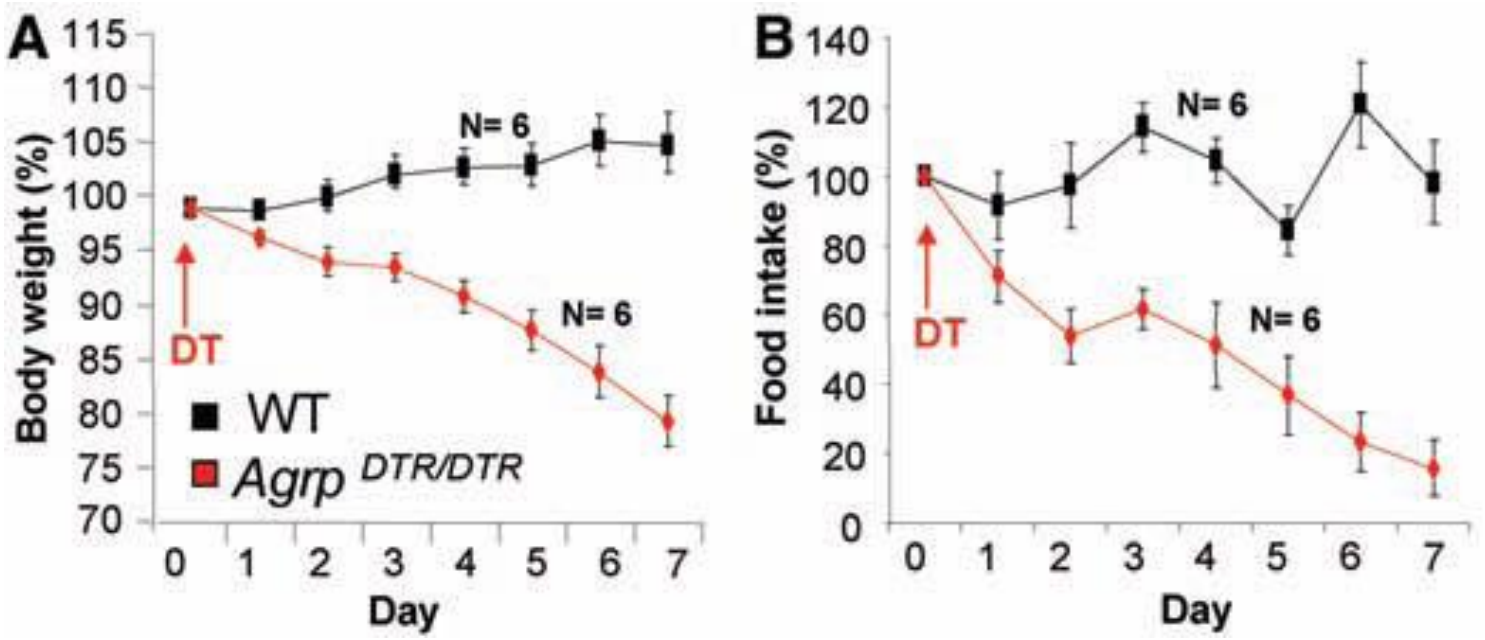




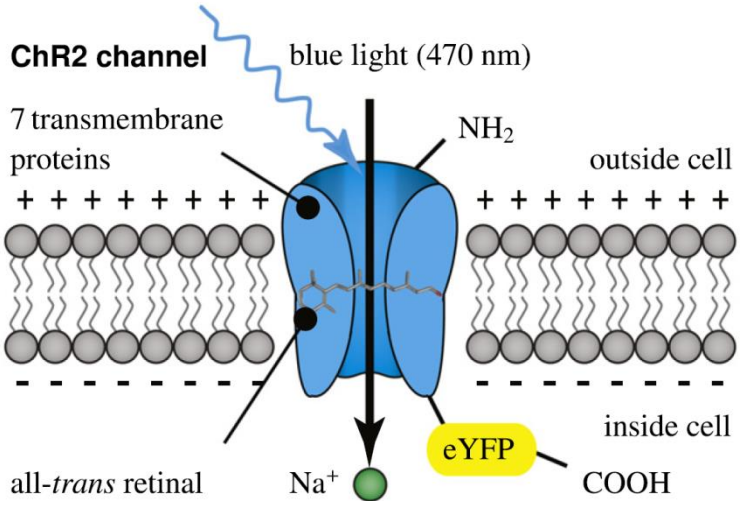


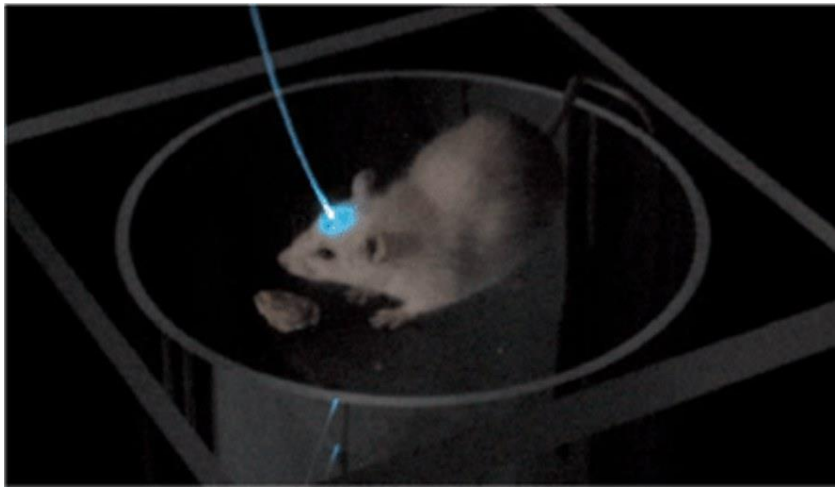
Ollmann et al., 1997


Diphtheria
toxin
POMC
Arcuate nucleus of the hypothalamus

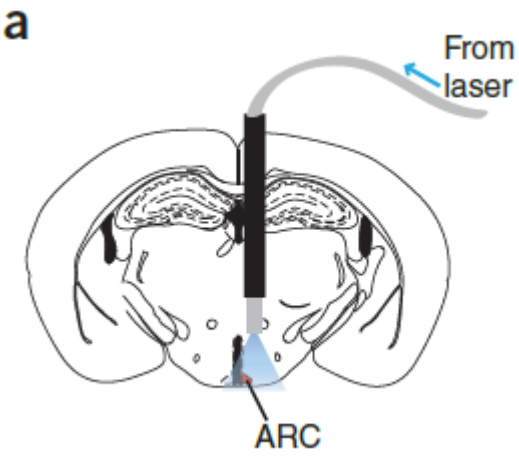


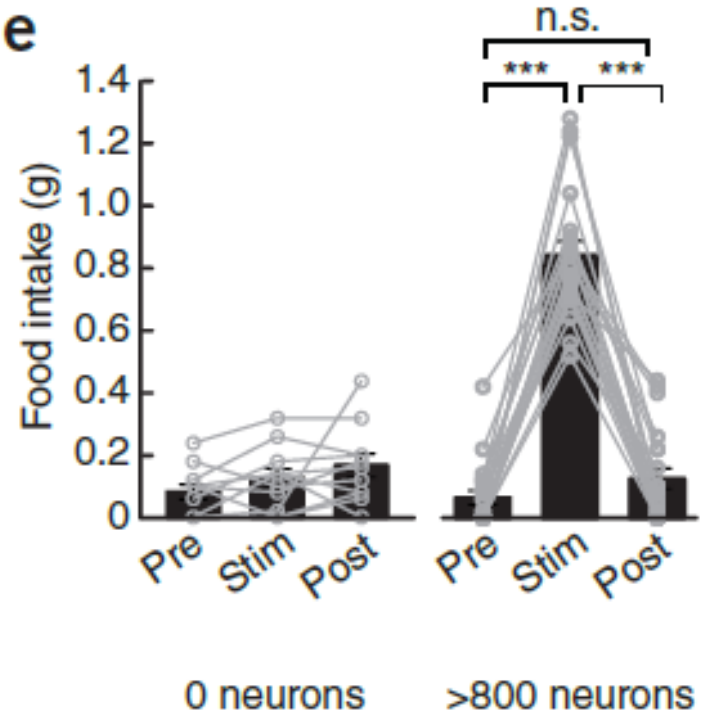
Luque et al. 2005

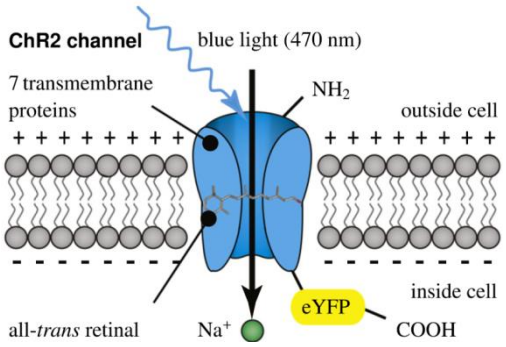

ChR2 channel
blue light (470 nm)
7 transmembrane proteins
NH_2
outside cell
+ + + + + + + +
+ + + + + + + +
- - - - - - - -
- - - - - - - -
inside cell
eYFP
COOH
all-*trans* retinal
Na^+



Optogenetic activation of AgRP neurons leads to binge eating

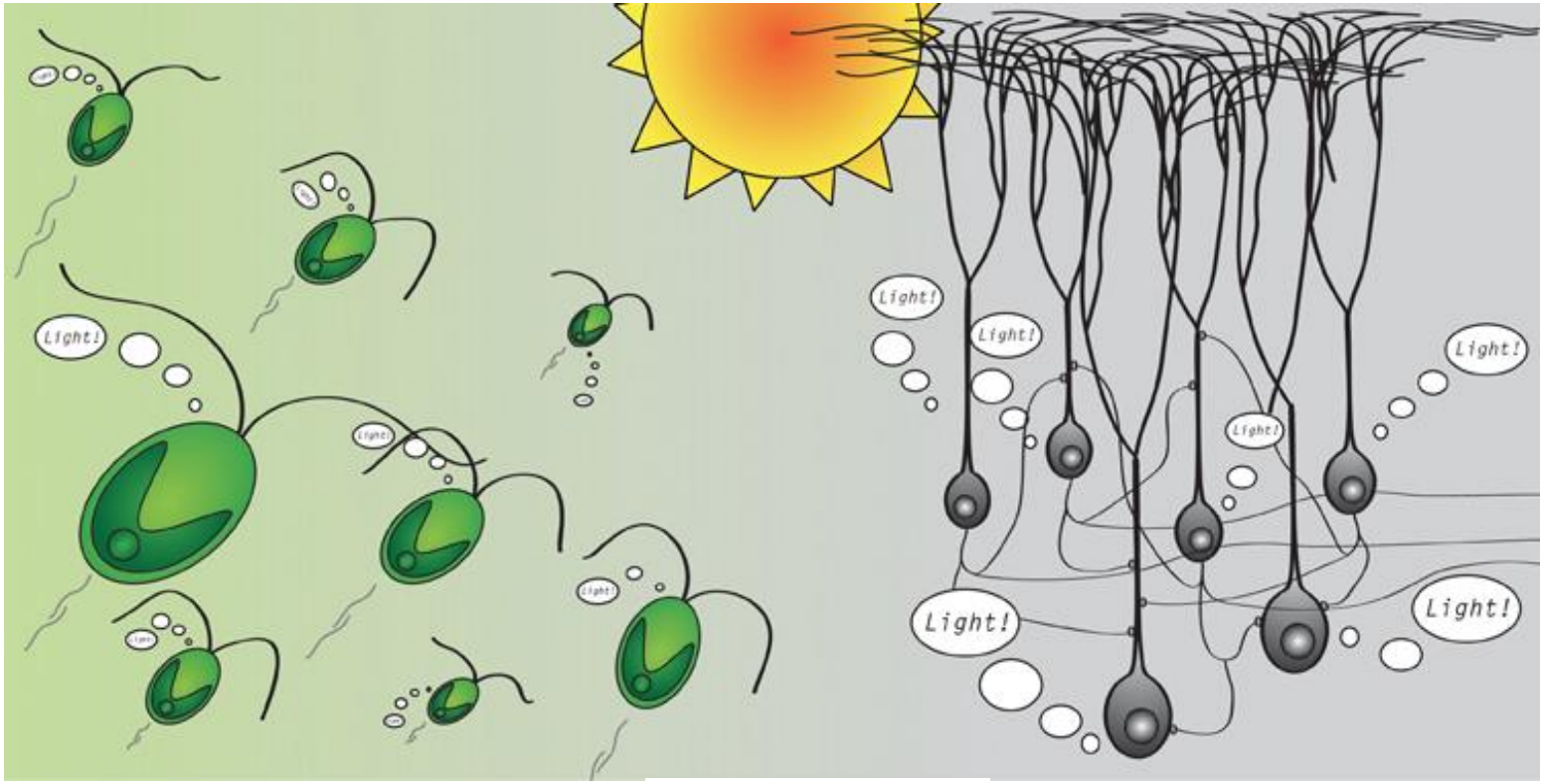




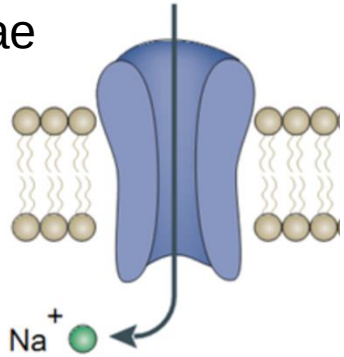


Aponte et al., 2011

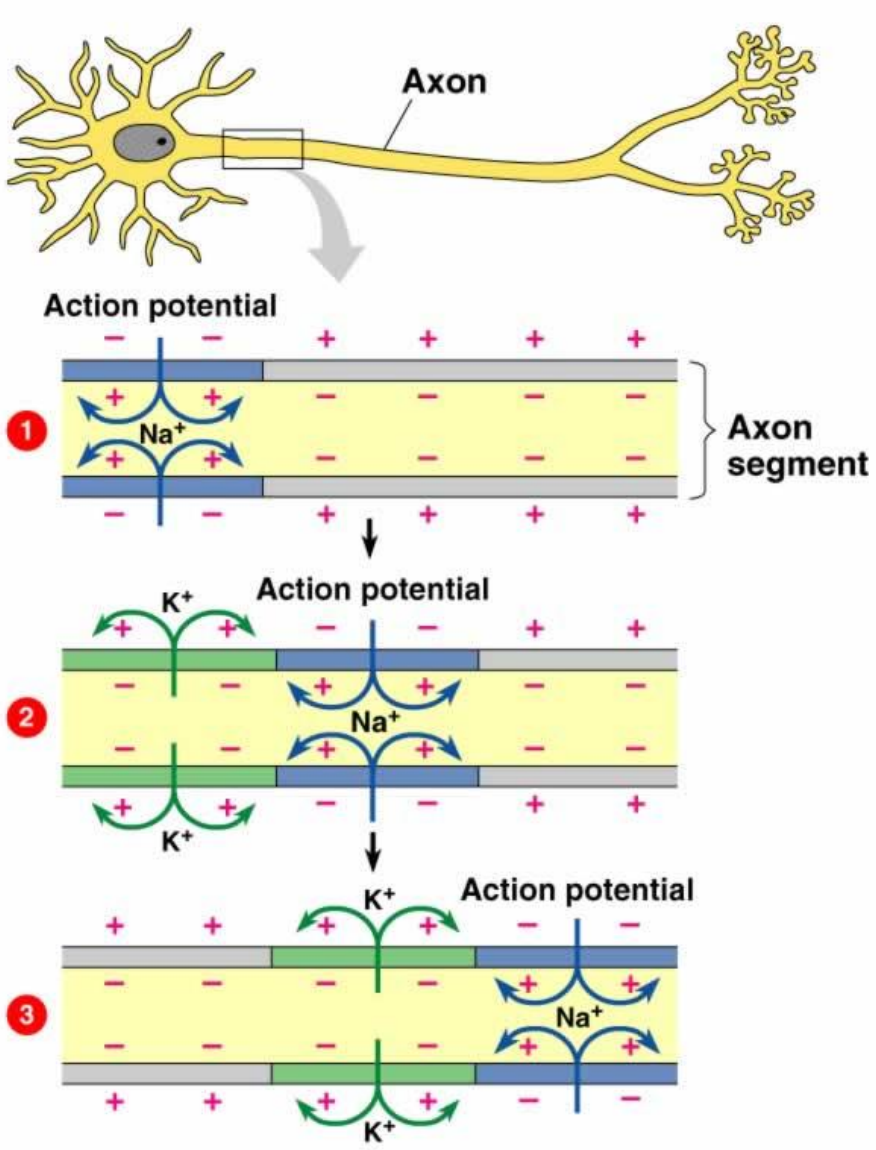
Optogenetics



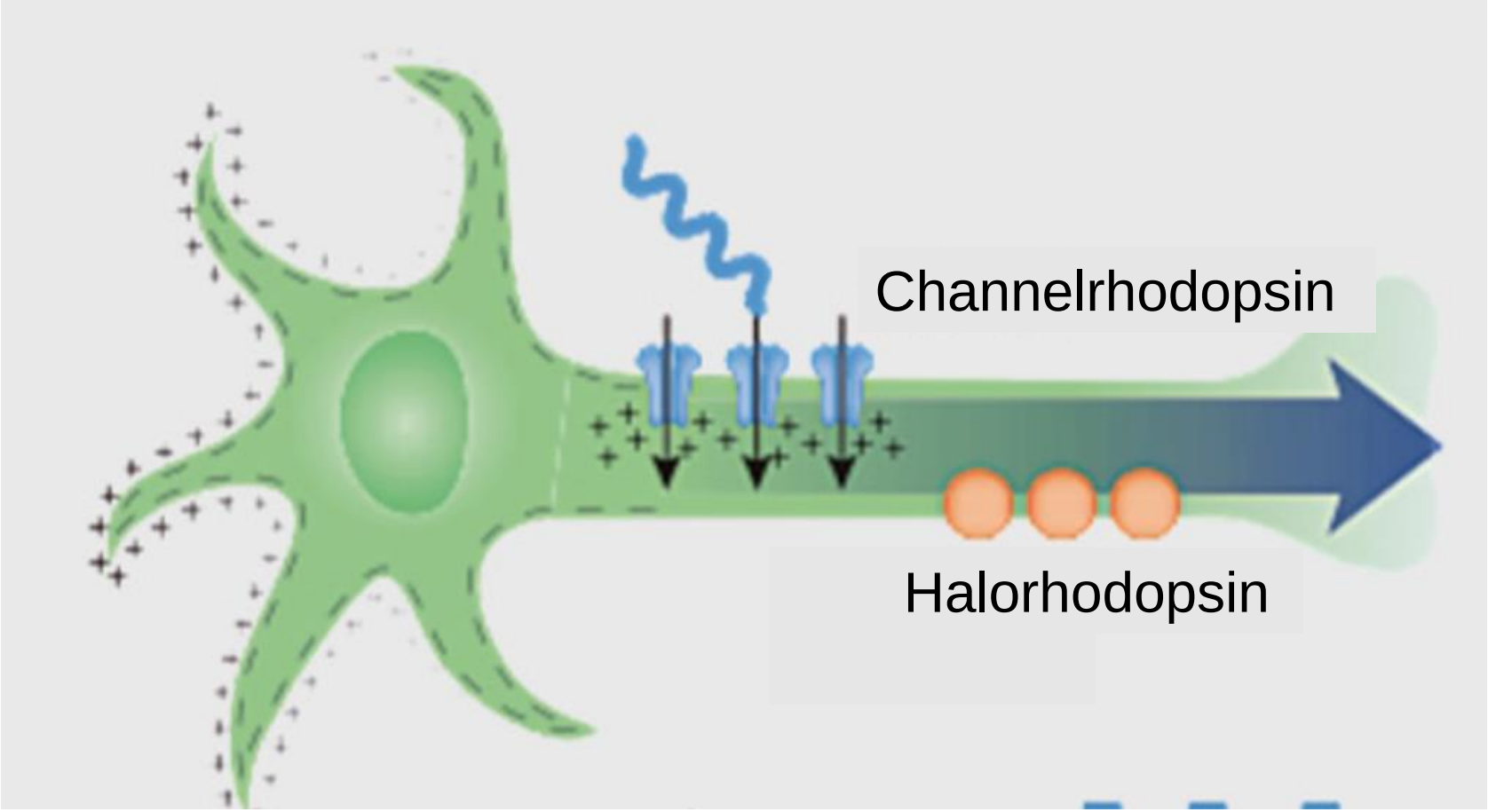
Light sensitive single-cell algae



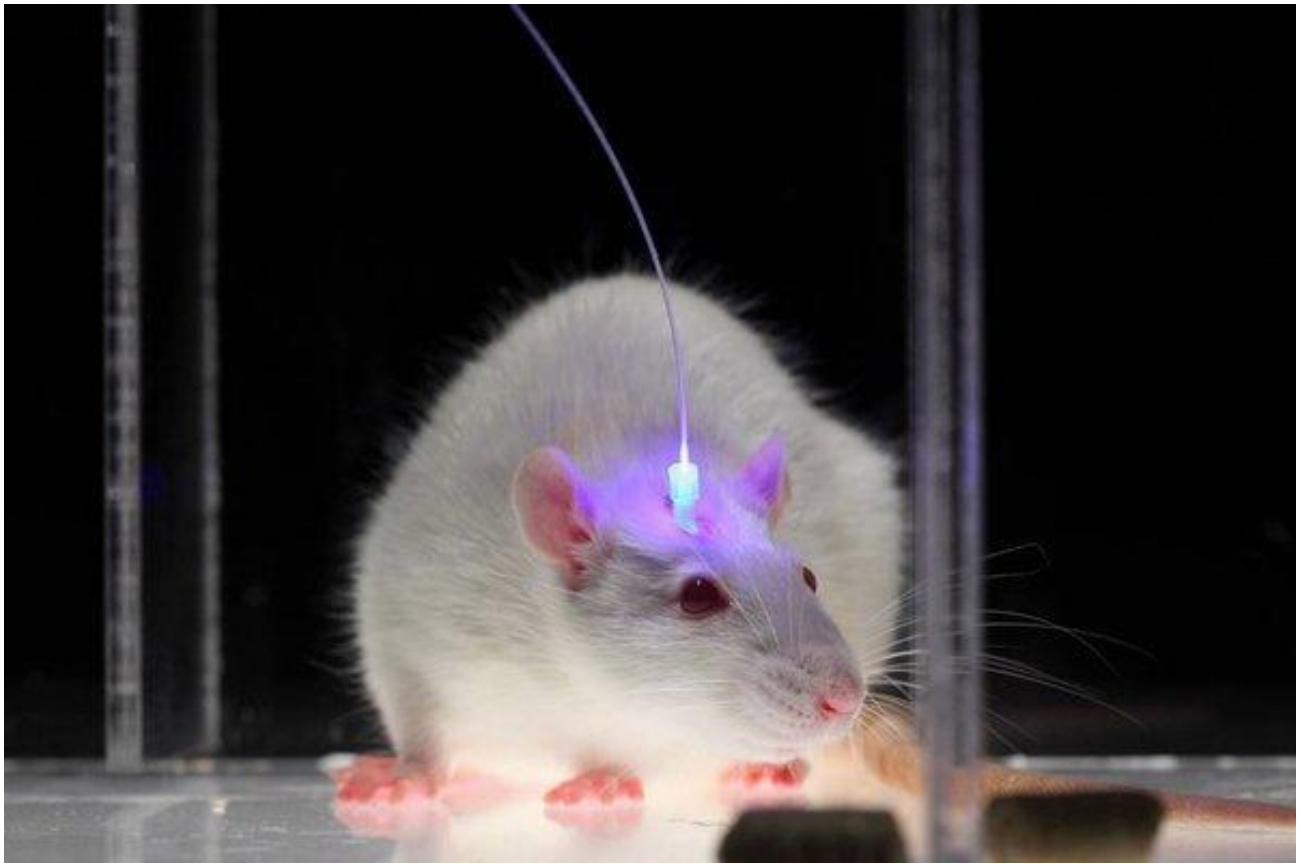
Light sensitive sodium channel called channelrhodopsin



Generation of action potential by light pulse



The blue-light sensitive Channelrhodopsin and the yellow light-activated chloride pump halorhodopsin together enable activation and silencing of neural activity

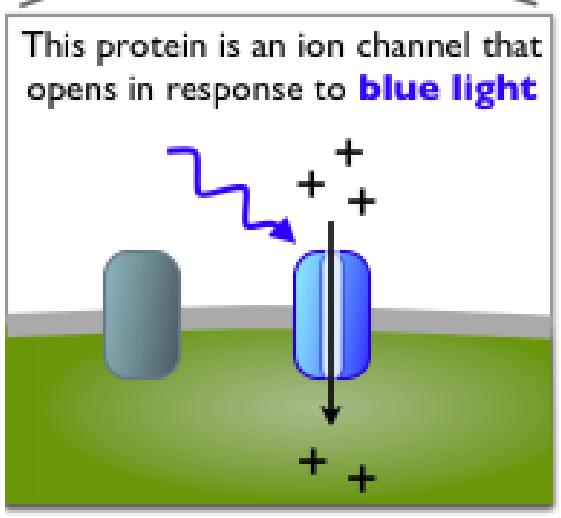


How optogenetics works

A light-sensitive protein from algae

Take the gene for this protein...

... and insert the DNA into specific neurons in the brain



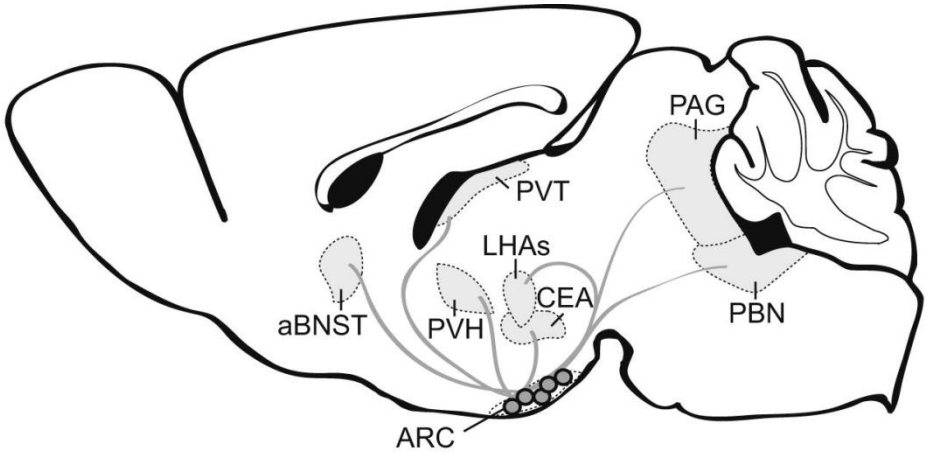
Neurons communicate by "**firing**." This is an electrical signal created by opening & closing ion channels.

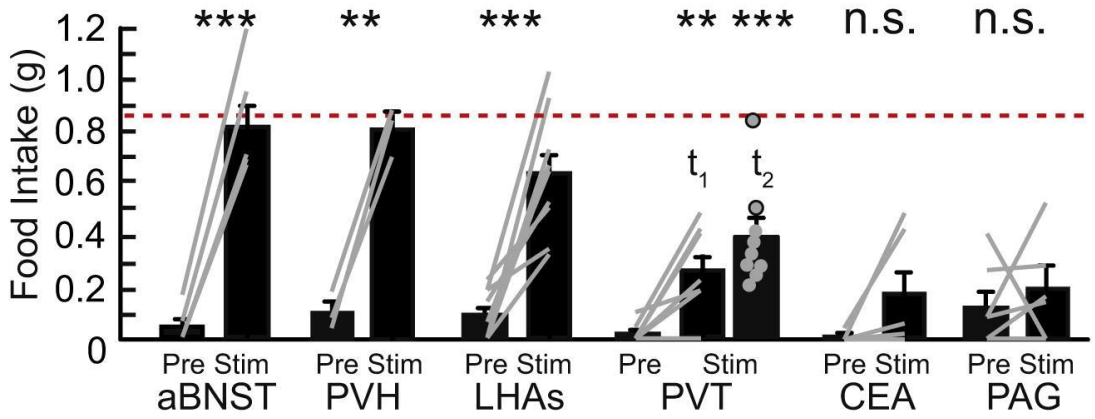
So now you can cause neurons to fire just by flashing **blue light!**

With the right combination of neurons, you can activate an entire brain circuit to control specific behaviors (like movement)

https://www.youtube.com/watch?v=I64X7vHSHOE
https://www.youtube.com/watch?v=rfEKc_0iaJo
https://www.youtube.com/watch?v=IW4j8_k8pmE

AgRP neurocircuitry



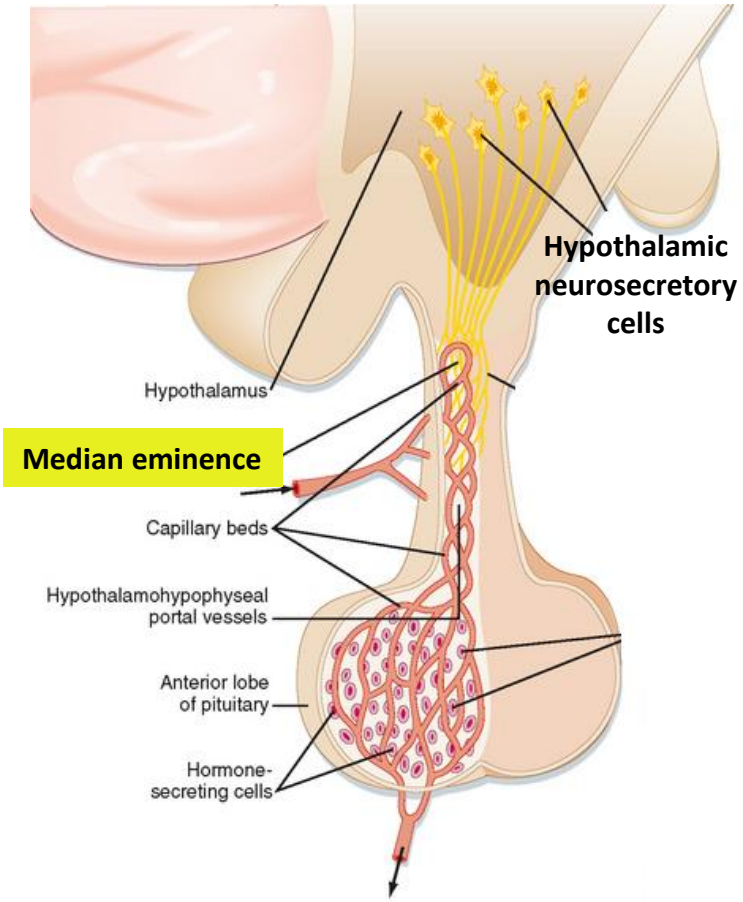


Betley *et al.* 2013

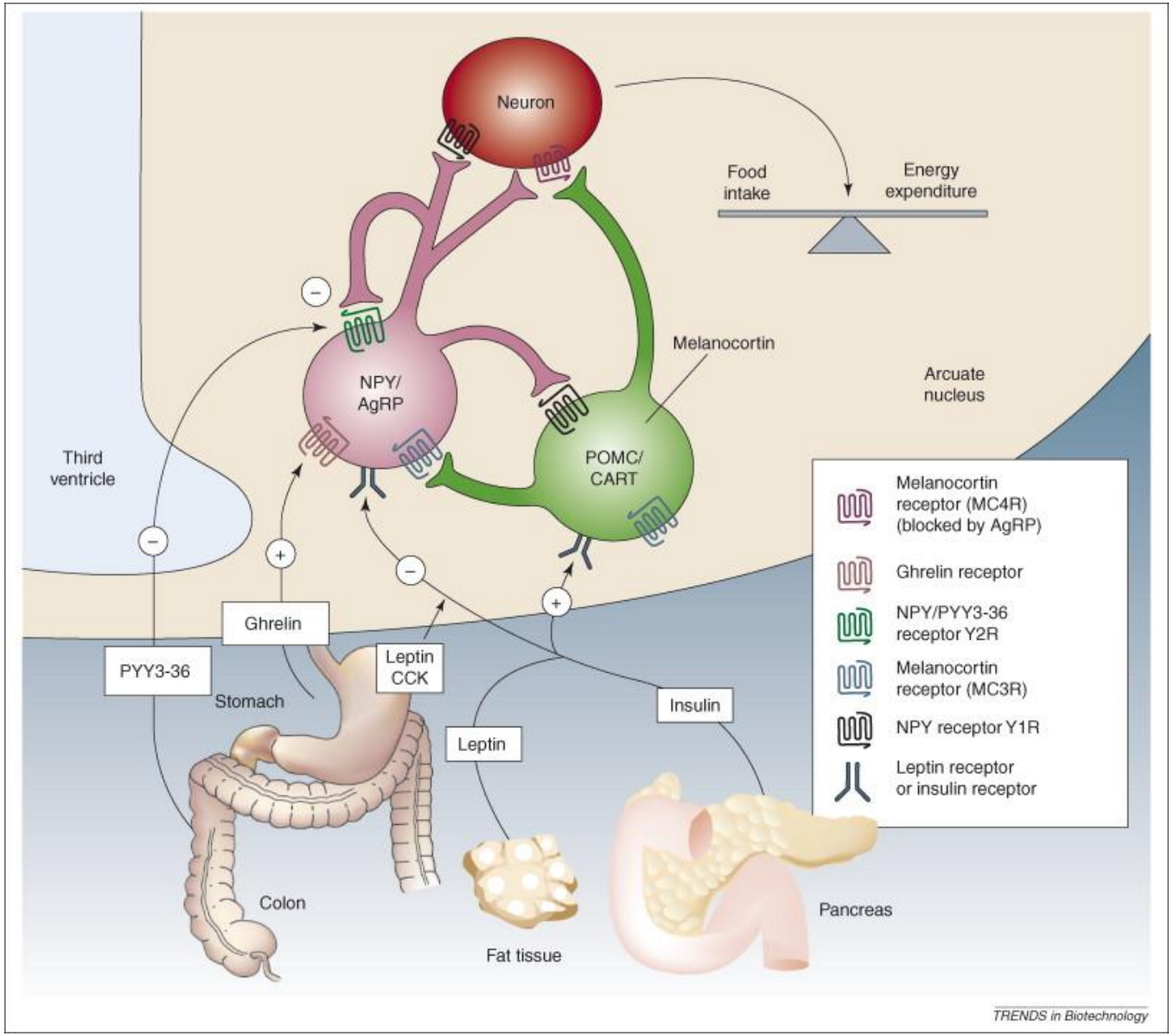
AgRP neurons innervate the pituitary

Table 1. Distribution and relative abundance of AGRP-immunoreactive fibers and terminals in the rat CNS

Anatomical sites	Agrp
Compact	–
Ventral part	+++
Dorsal hypothalamic area	++
Lateroanterior hypothalamic nucleus	+
Lateral hypothalamic area	+++
Ventrolateral hypothalamic nucleus	++
Perifornical nucleus	++++
Posterior hypothalamic area	+
Arcuate nucleus	+++++
Median eminence, internal part	+++
Median eminence, external part	+
Medial tuberal nucleus	++
Supramammillary nucleus	+



Bangol *et al*. 1999


Neuron
Food intake
Energy expenditure
Melanocortin
Arcuate nucleus
NPY/ AgRP
POMC/ CART
Third ventricle
Ghrelin
PYY3-36
Leptin CCK
Stomach
Insulin
Leptin
Colon
Fat tissue
Pancreas
Melanocortin receptor (MC4R) (blocked by AgRP)
Ghrelin receptor
NPY/PYY3-36 receptor Y2R
Melanocortin receptor (MC3R)
NPY receptor Y1R
Leptin receptor or insulin receptor
TRENDS in Biotechnology

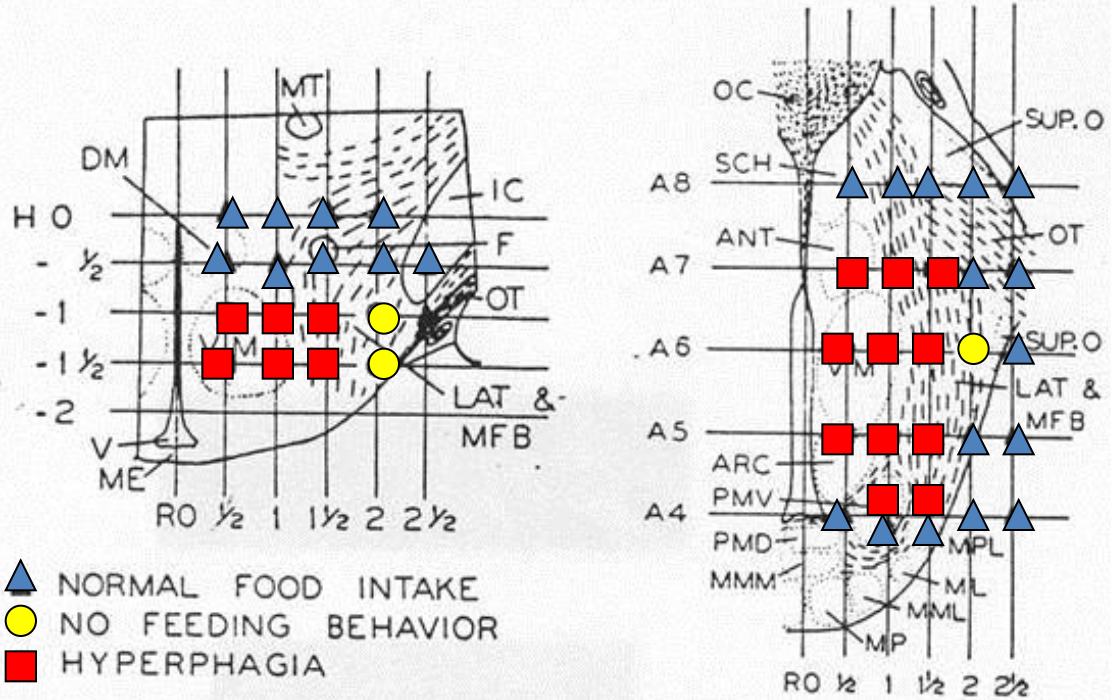


FIGURE 15-4. Cross section of a rat's hypothalmus at level of the ventromedial nucleus (*left*) and of the same side in a horizontal plane, also at the level of the ventromedial nucleus (*right*). Horsley-Clarke coordinates are superimposed. The feeding behavior of rats with small bilaterally symmetrical lesions in each area is indicated. (From Anand and Brobeck,[16] courtesy of *Yale J. Biol. Med.*)

Summary

1. α-MSH acts as an agonist of MC4R. It reduces food intake and increases energy expenditure.
2. Agouti protein is naturally expressed in skin tissue and regulates pigmentation. Its overexpression in brain tissue leads to obesity due to antagonistic effect on MC4R.
3. Agouti related peptide (AgRP) is expressed in the hypothalamus.
4. AgRP expression is elevated when energy stores are low (for example- low leptin).
5. AgRP acts as an antagonist of MC4R. It reduces energy expenditure and increases food consumption.
6. Activation of AgRP neurons leads to rapid feeding behavior while their ablation cause self starvation.

- What will be the phenotype of AgRP KO mice?
- What will be the phenotypes of cell-type specific KOs of the leptin receptor in mice?
  One in hypothalamic AgRP neurons
  One in hypothalamic POMC neurons

- A mice line was made by crossing ob/+ and db/+. Offspring that are ob/+,db/+ were collected and breed. What will be the result? What % of fat mice will there be?