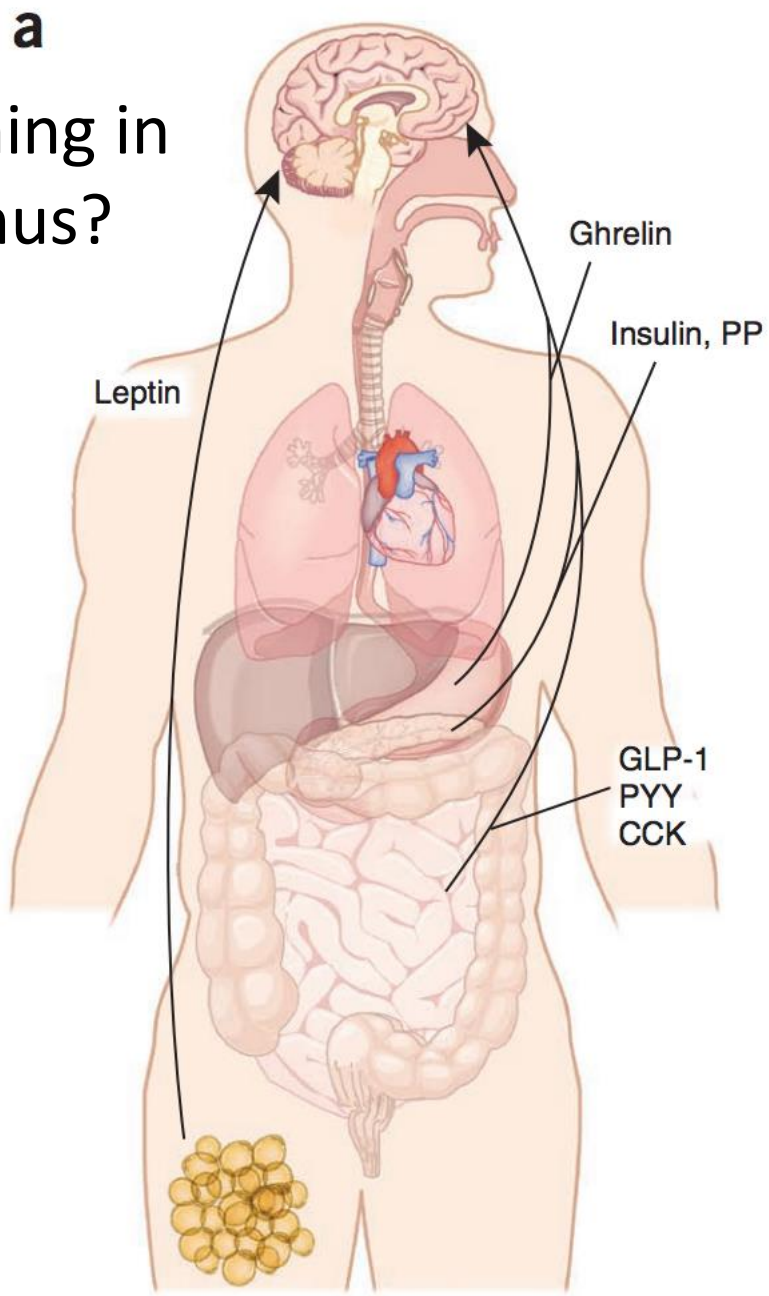
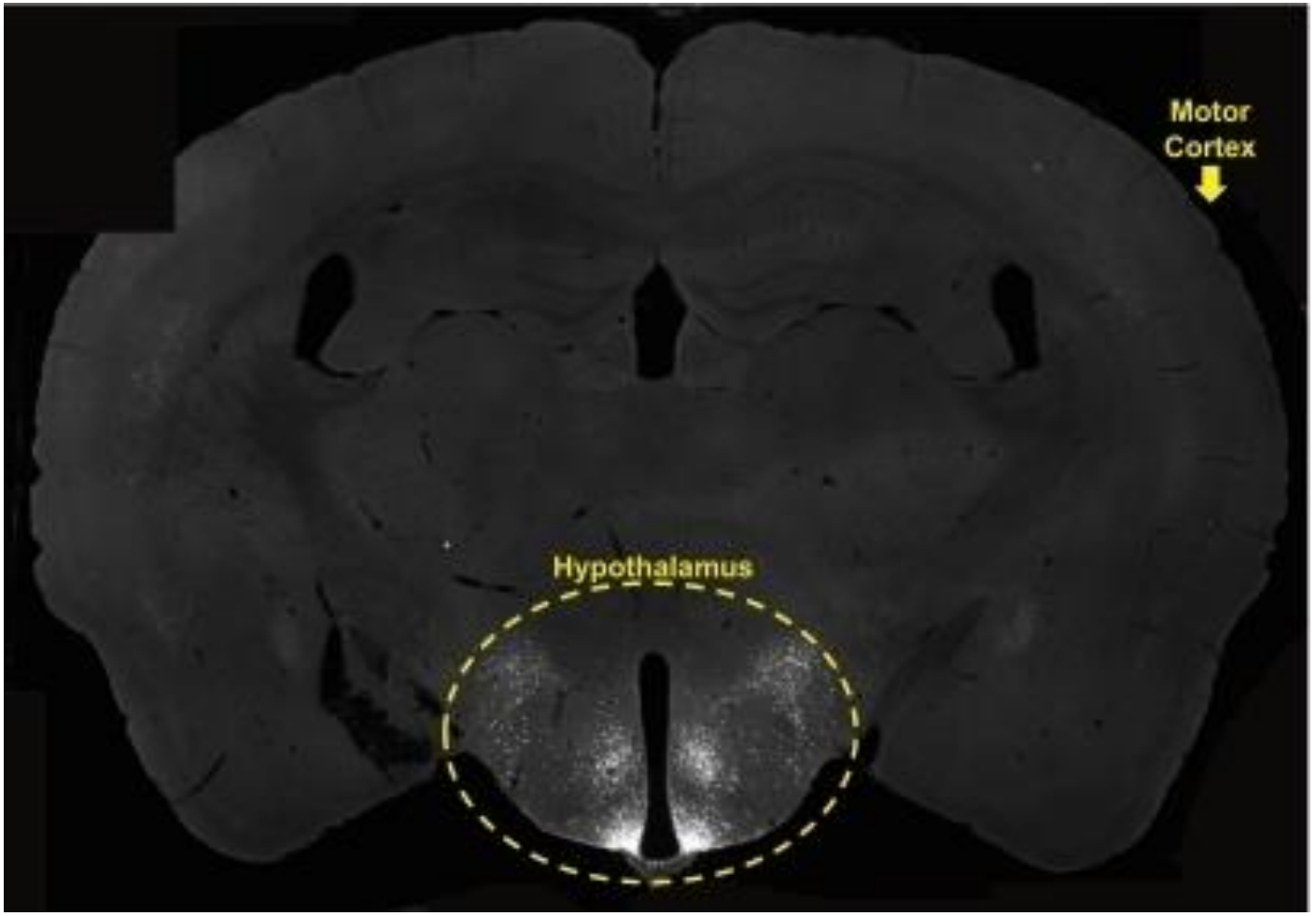
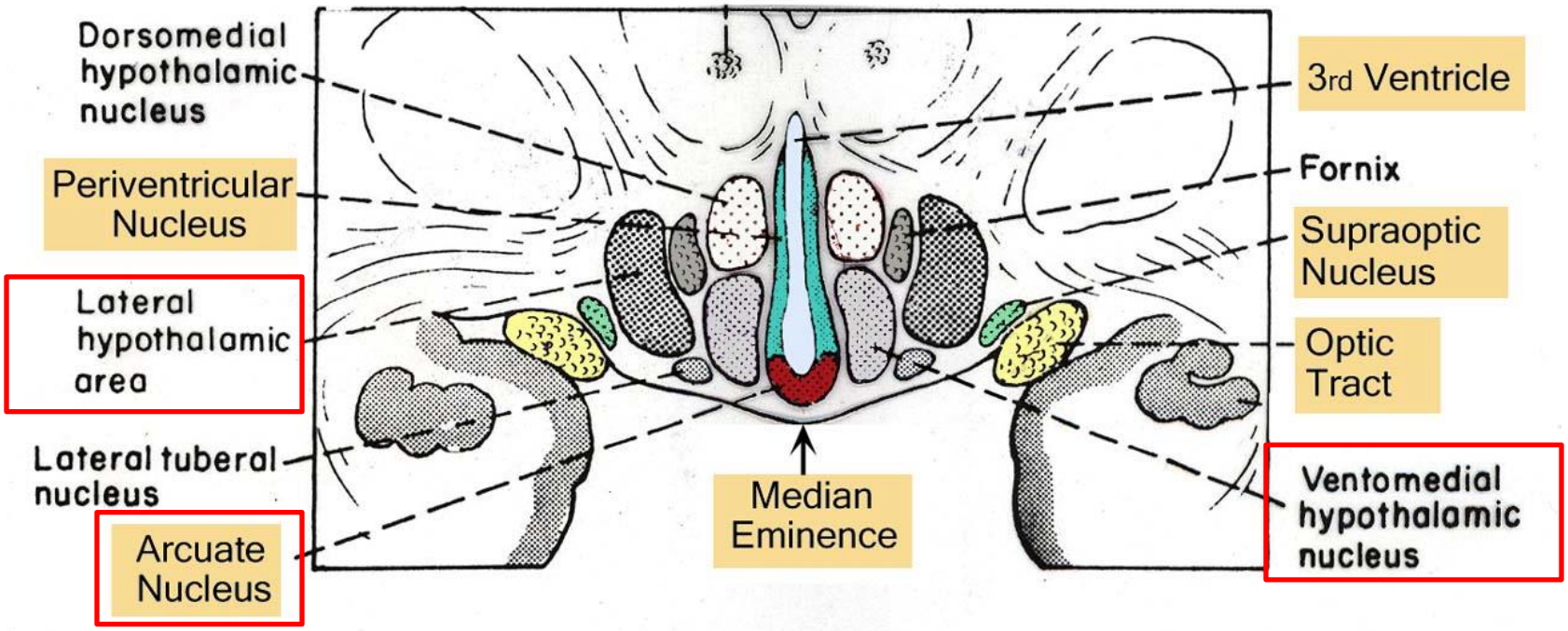
What is happening in the hypothalamus?

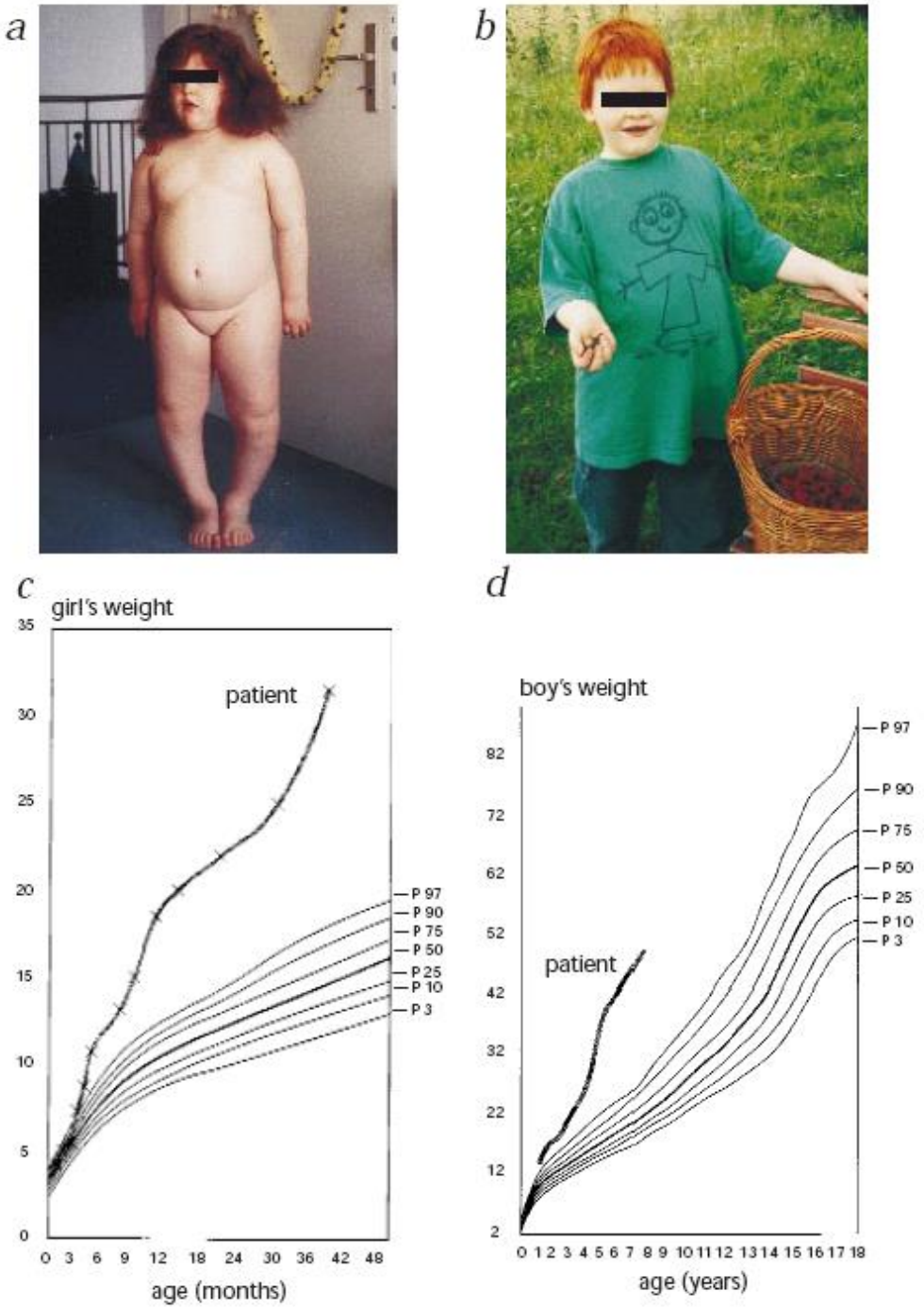


Leptin receptor–expressing neurons in the mouse hypothalamus



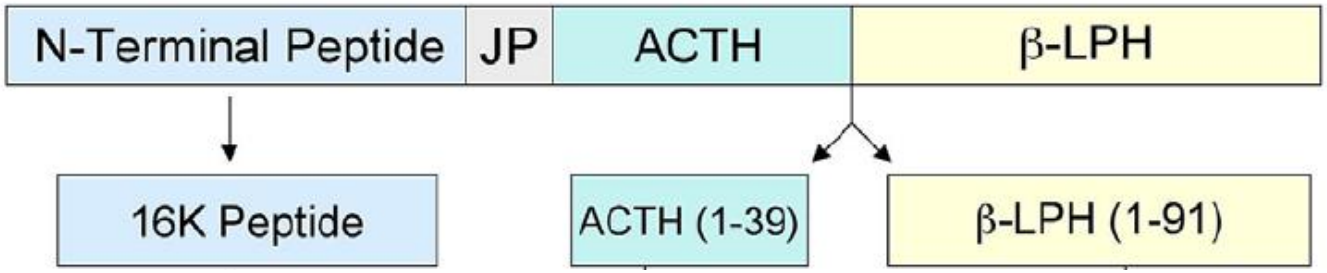
Hypothalamic Nuclei



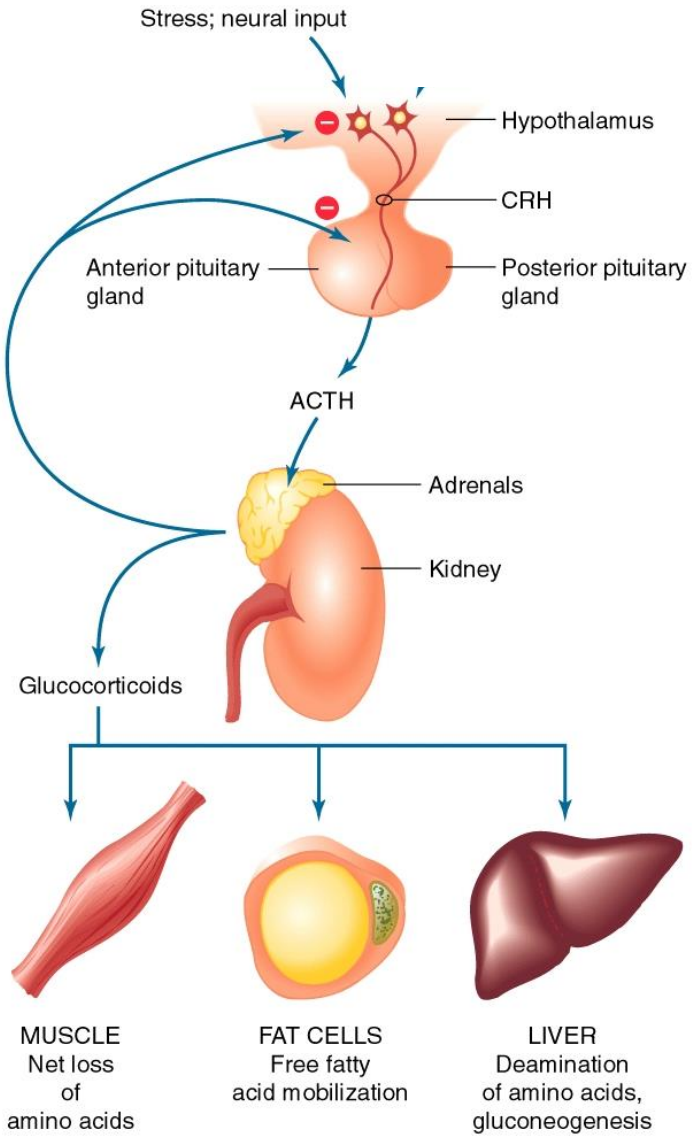


Krude et al., 1998

PROOPIOMELANOCORTIN (POMC)



Pituitary

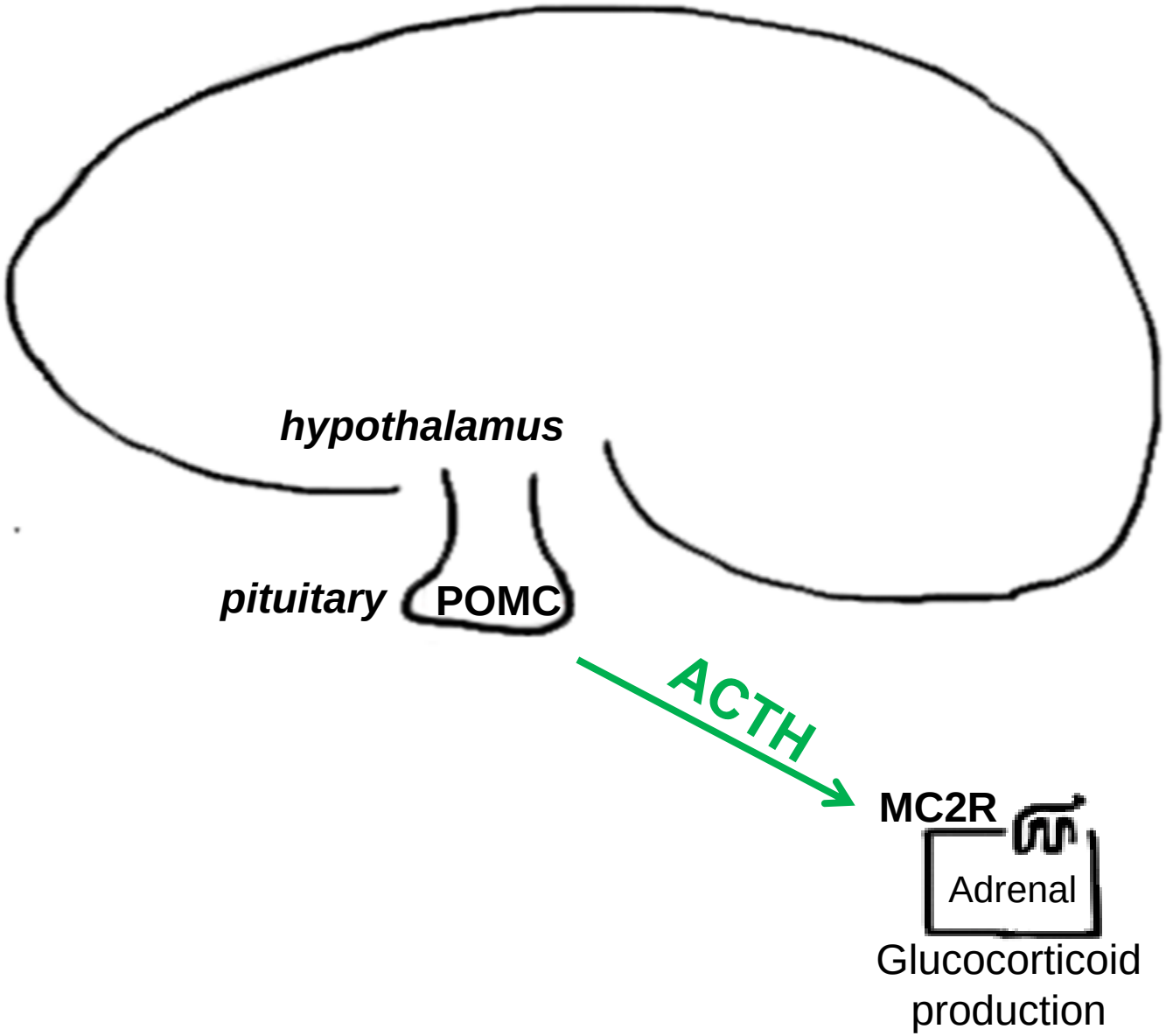


CRH – corticotropin releasing hormone

ACTH – corticotropin; adrenocorticortrophic hormone

Glucocorticoids, cortisol or corticosterone

POMC functions in the stress response



Pituitary

Hypothalamus and hair follicle

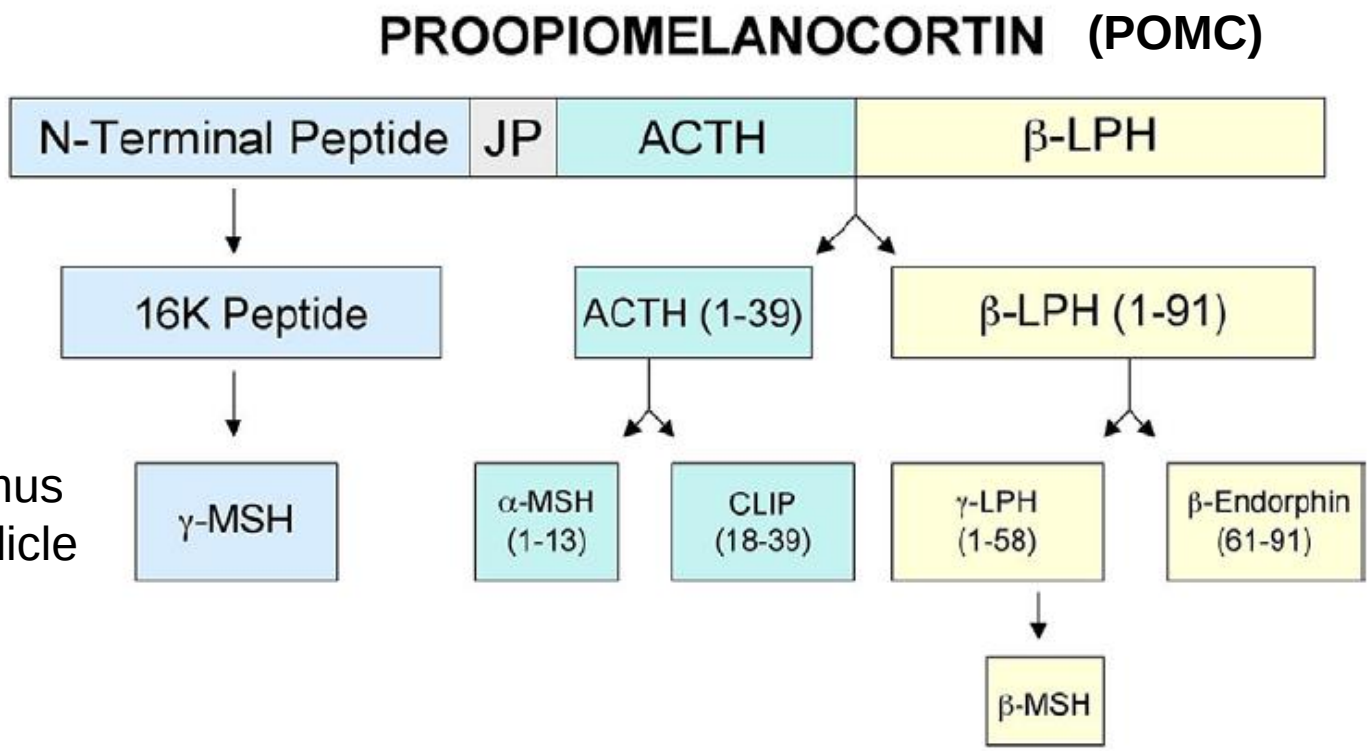
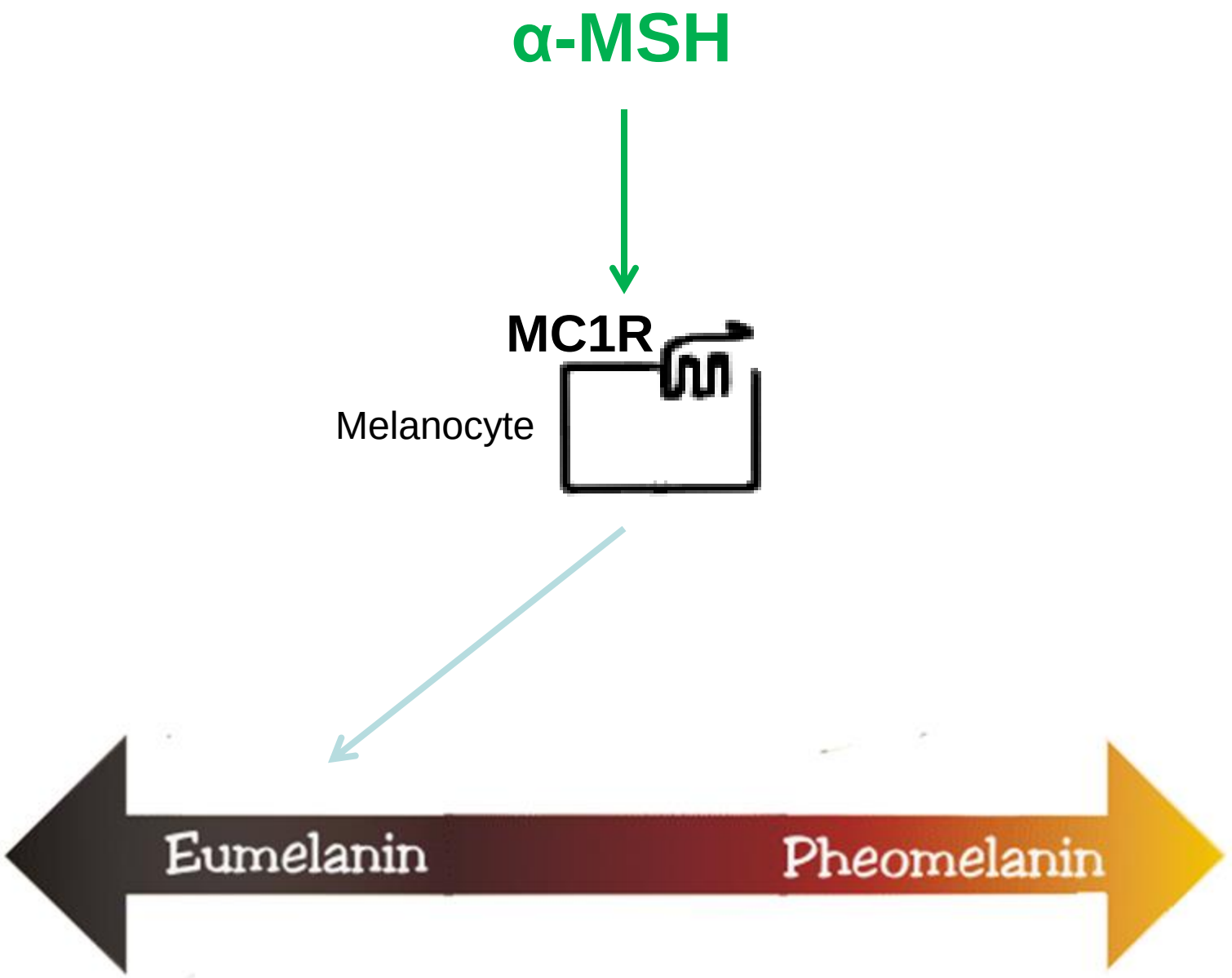
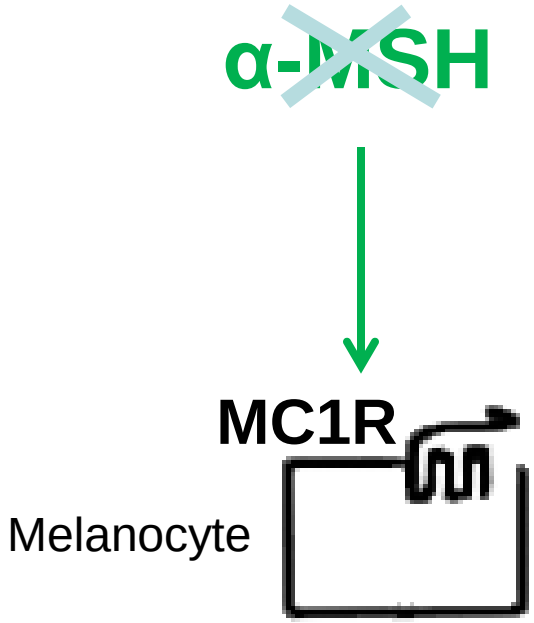


Figure 2. Schematic diagram of the POMC precursor molecule and the major peptide products which are derived from this precursor by endoproteolytic cleavage. (JP = Joining peptide; LPH= Lipotropin; CLIP= corticotropin-like-intermediate lobe peptide).


α-MSH
MC1R
Melanocyte
Eumelanin
Pheomelanin


α-MSH
MC1R
Melanocyte


Eumelanin
Pheomelanin

α-MSH

MC1R

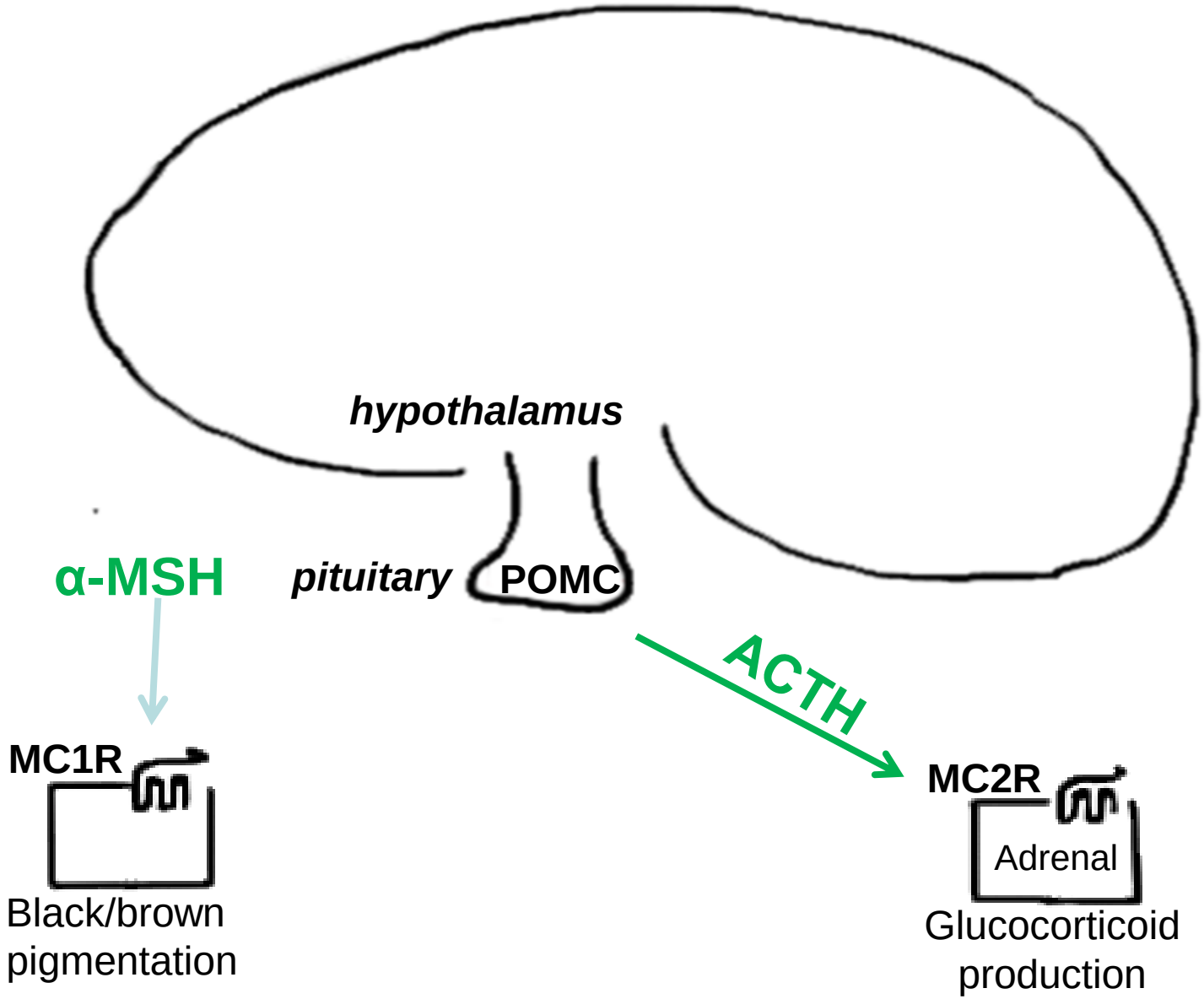
Melanocyte

Red pigmentation

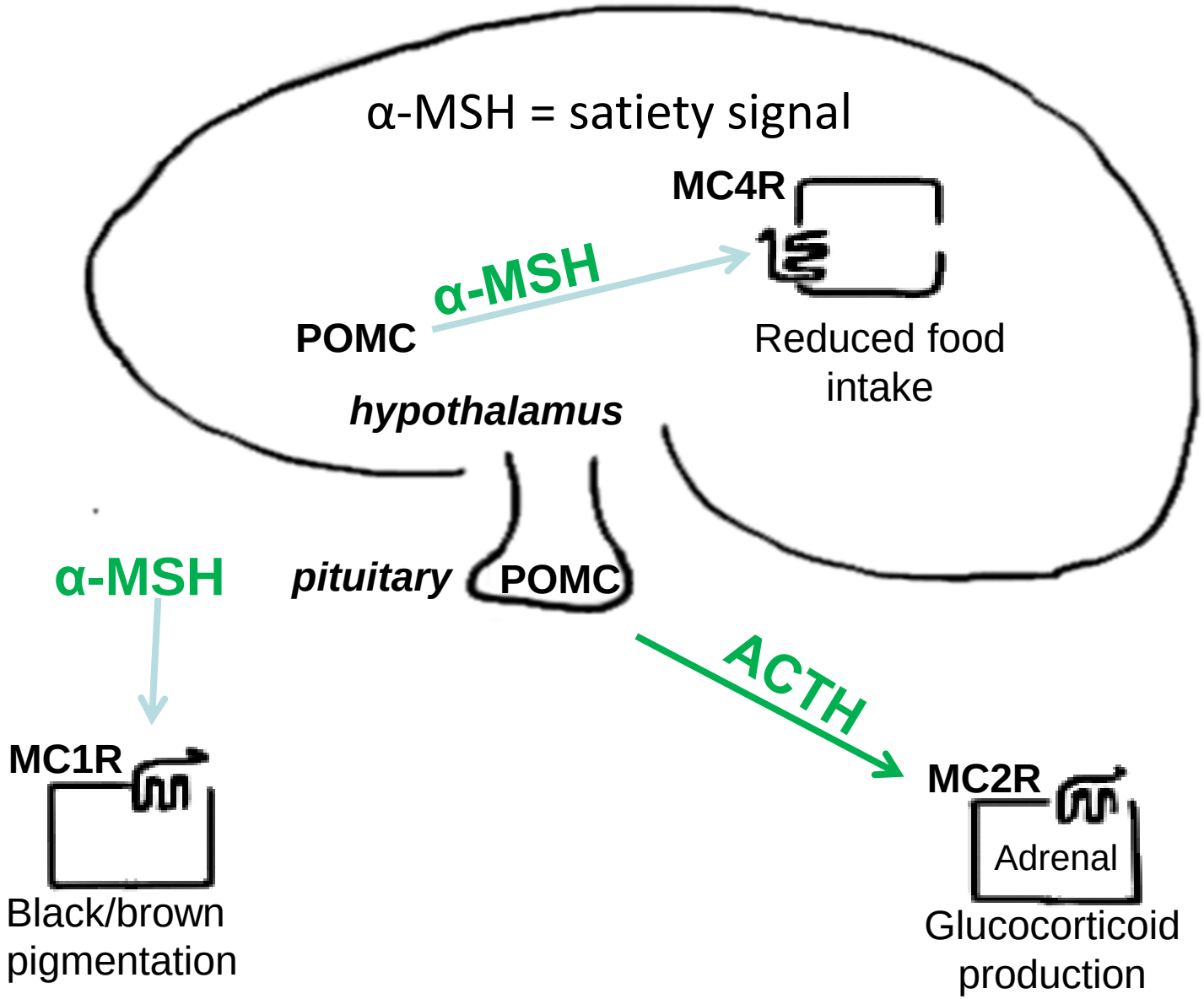
Eumelanin

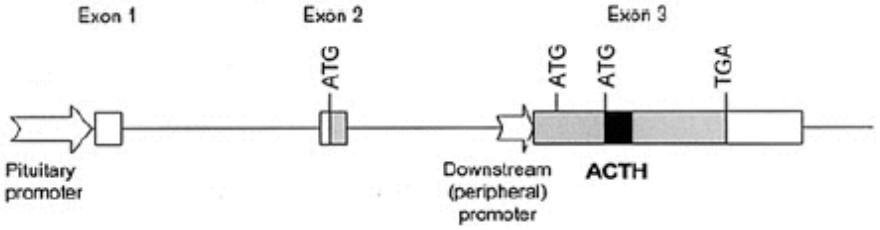
Pheomelanin

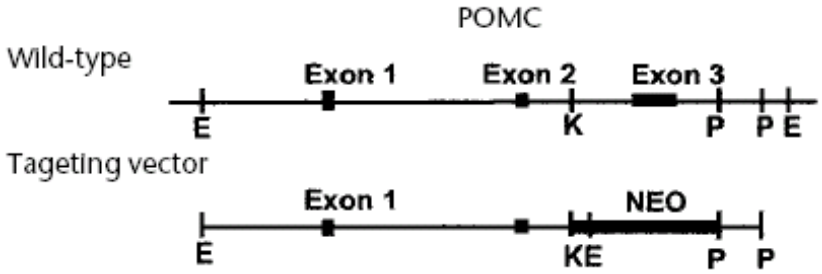
POMC functions in the stress response, pigmentation

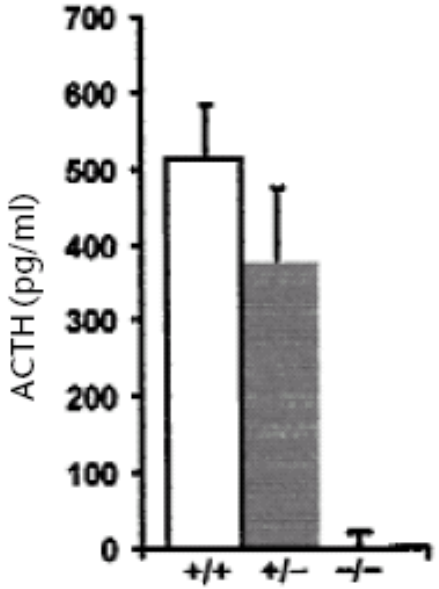


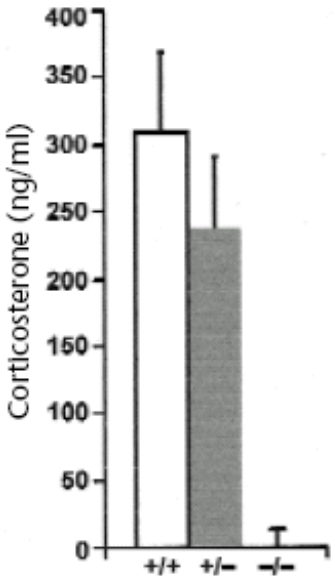
POMC functions in stress response, pigmentation and food consumption









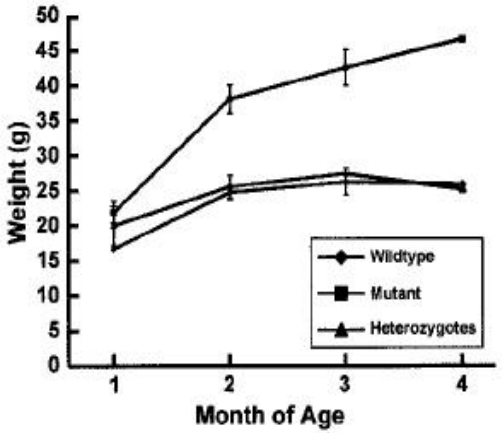


Yaswen et al., 1999

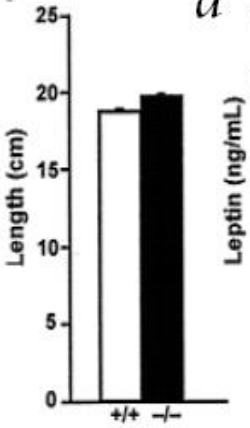
a

–/– +/+

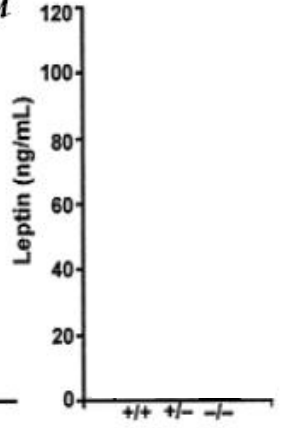
b



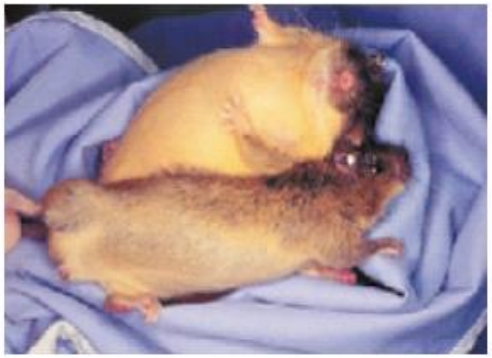
c



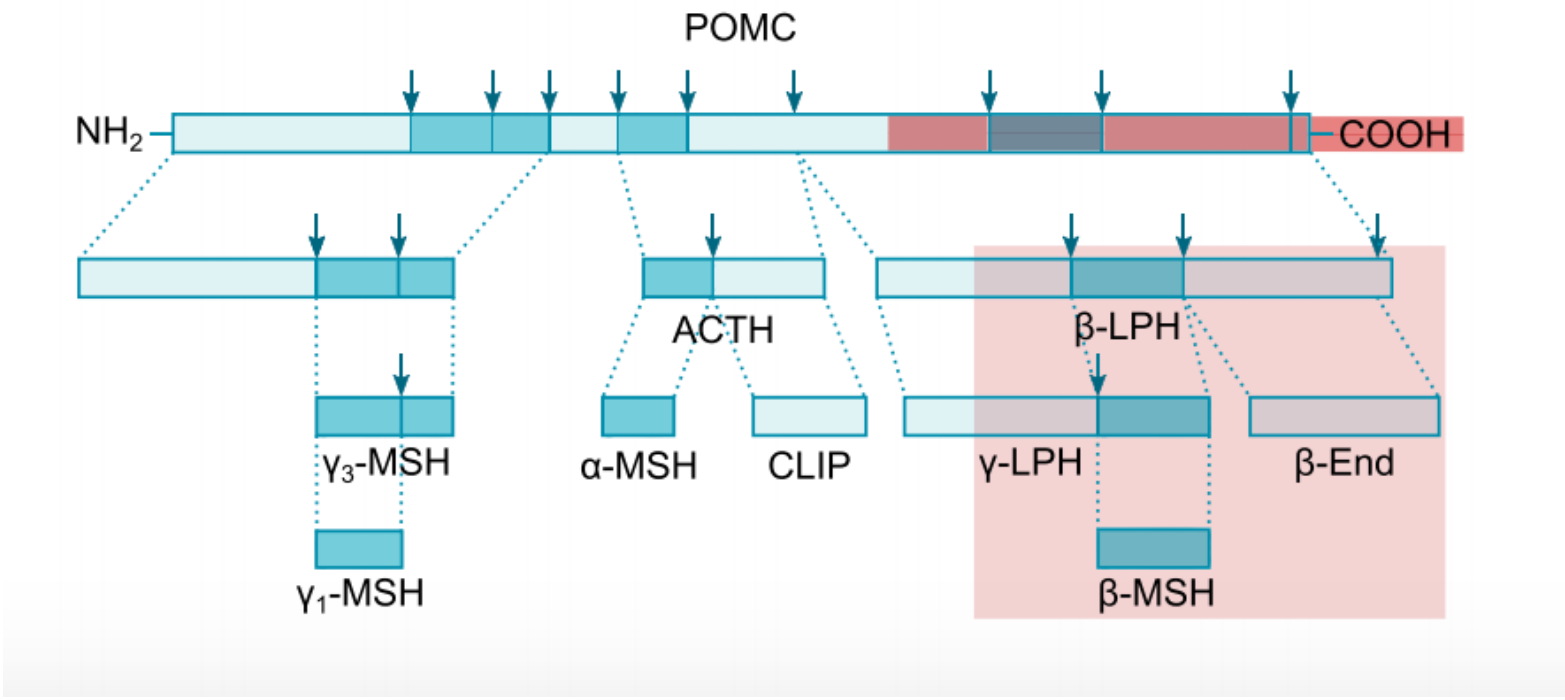
d

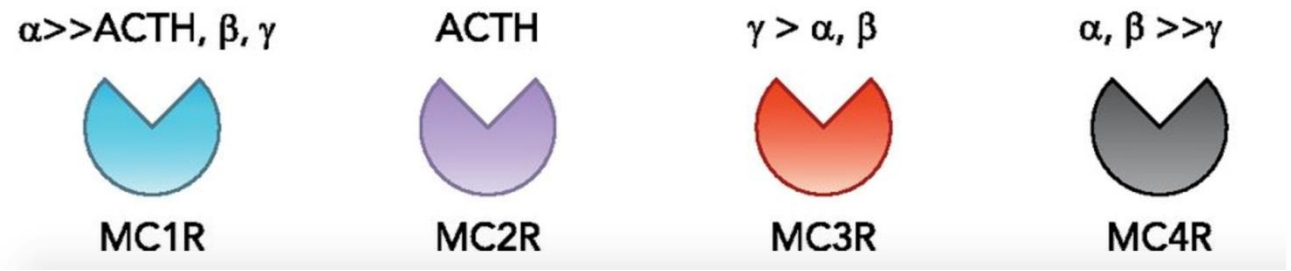


g



Yaswen et al., 1999

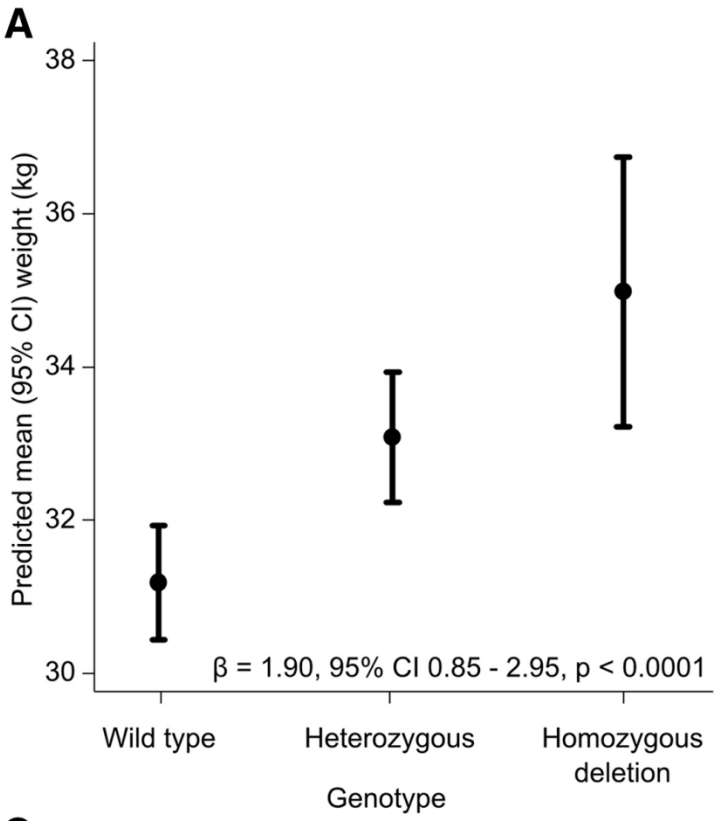


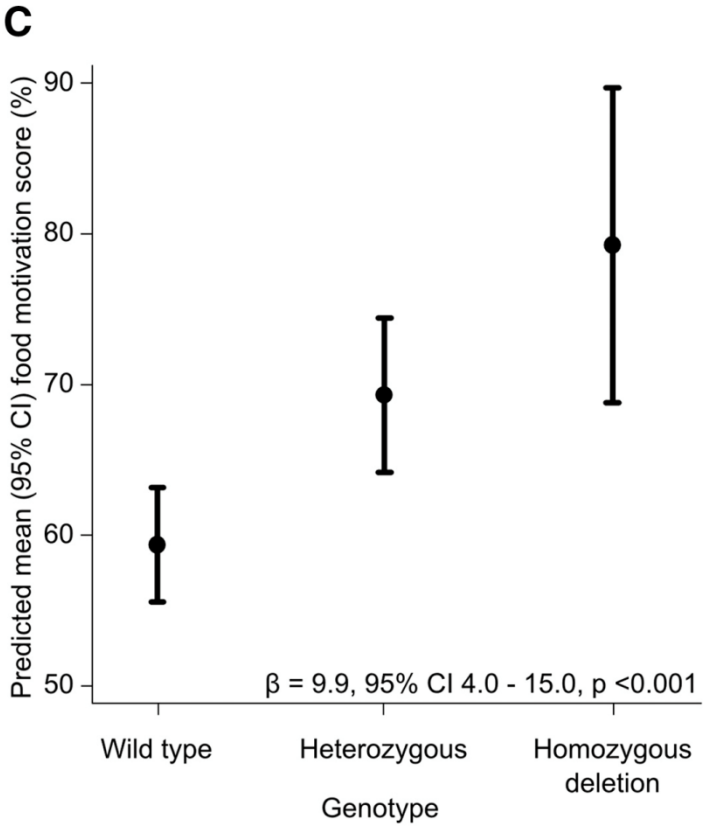


Raffan et al. 2016 *Cell Metabolism*

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],





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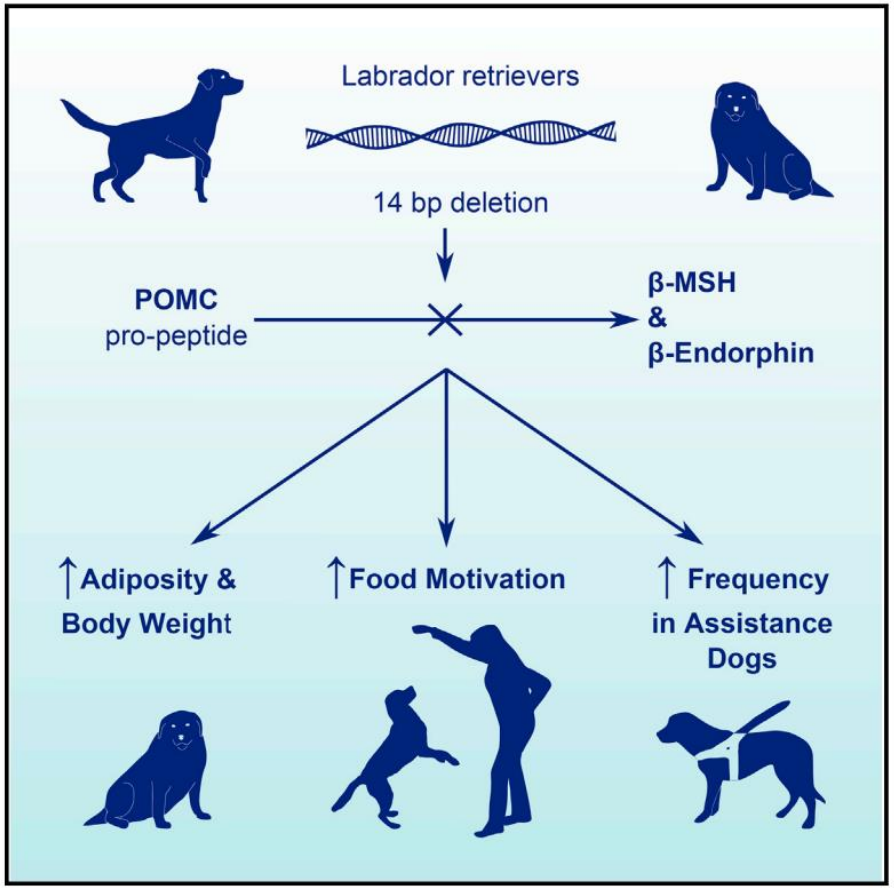
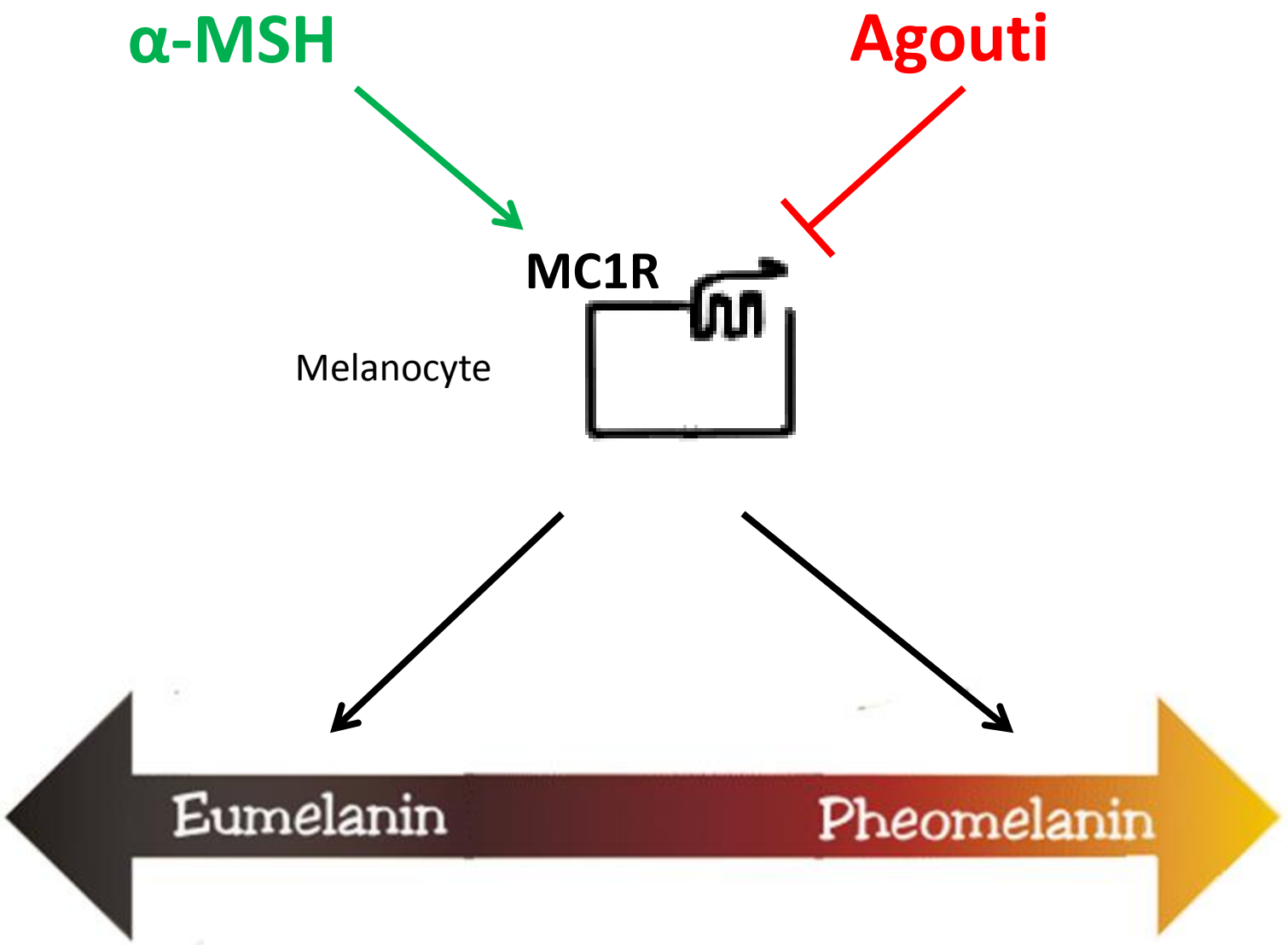
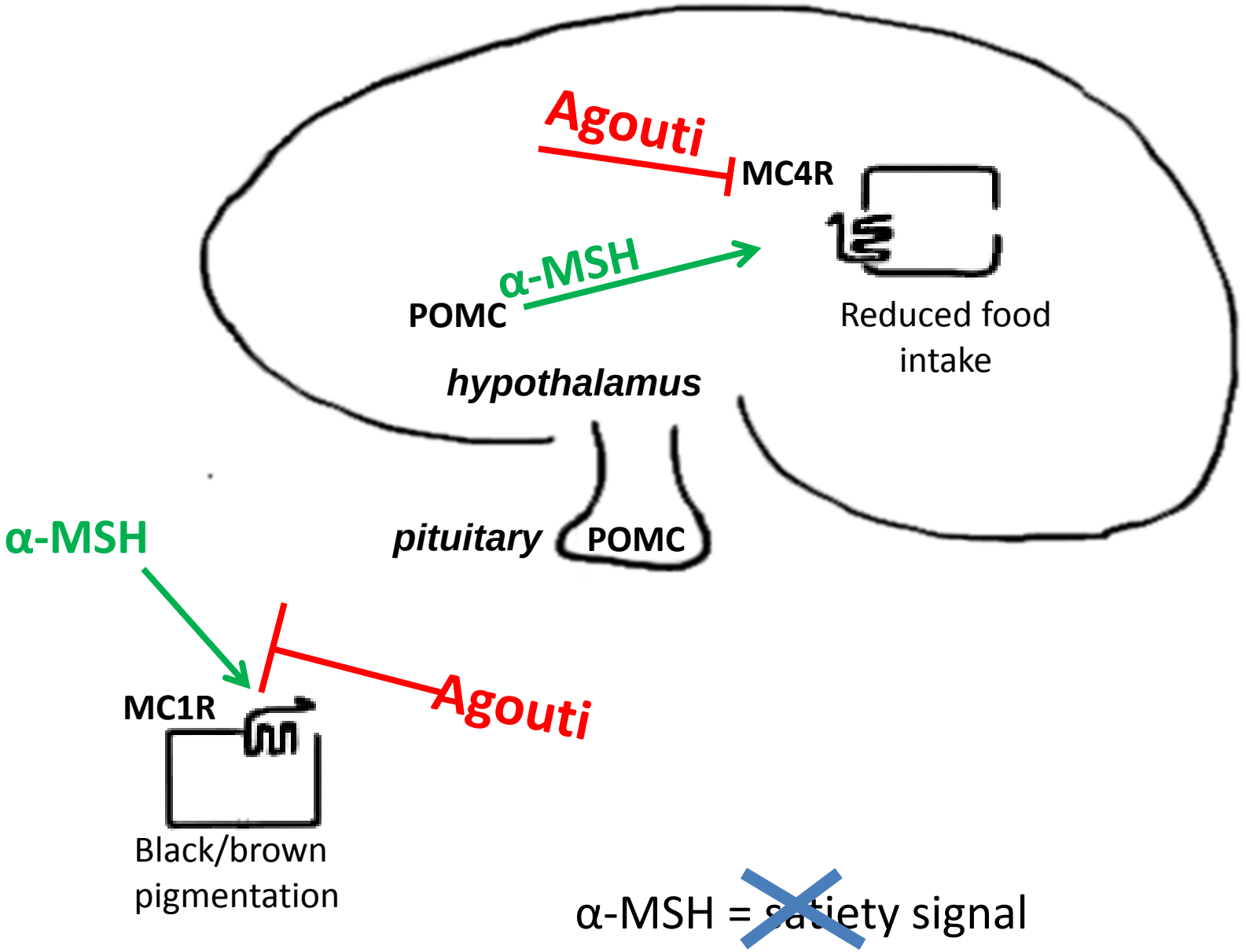


http://www.cam.ac.uk/research/news/genetic-variant-may-help-explain-why-labradors-are-prone-to-obesity

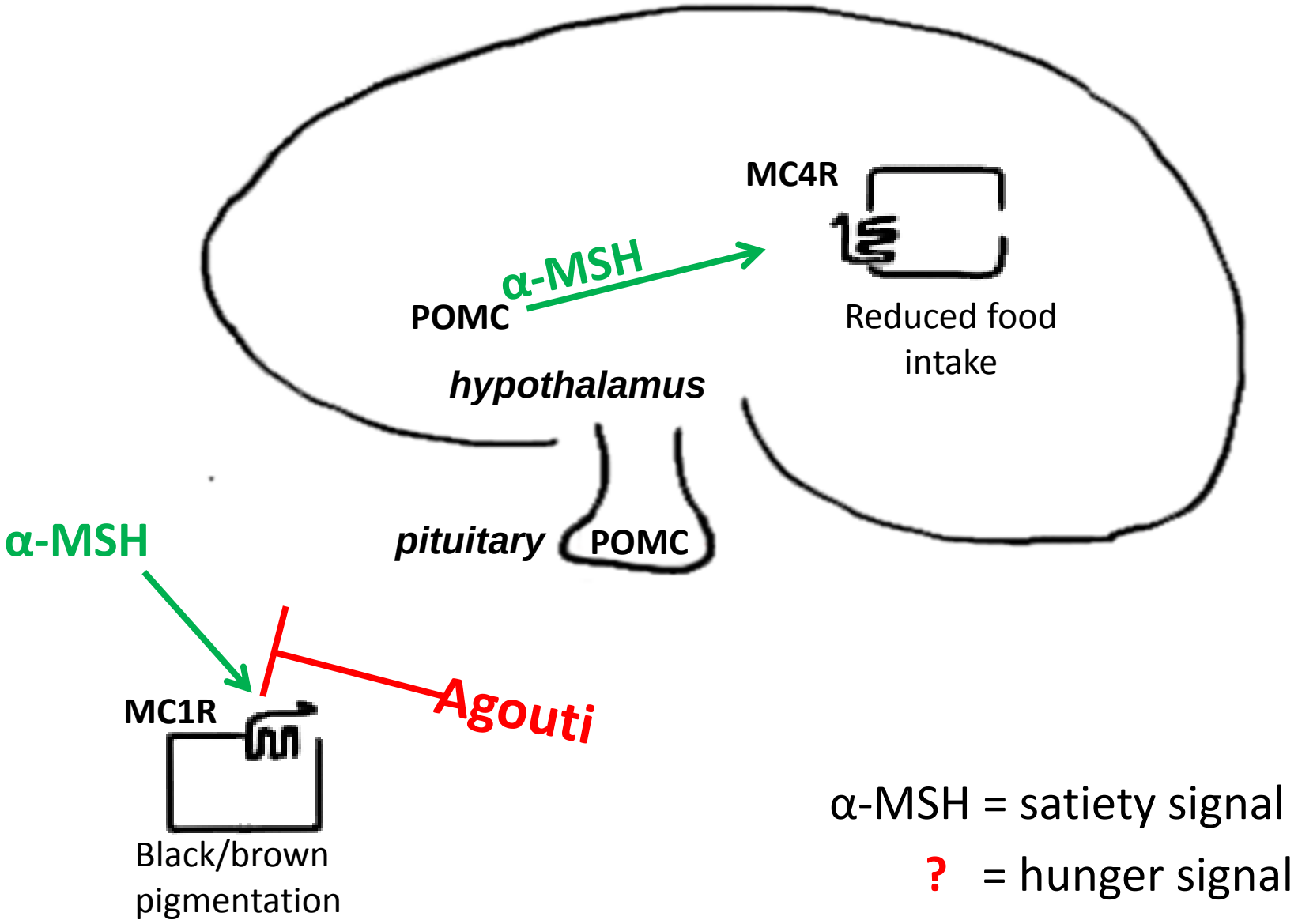
A^y mutation


α-MSH
Agouti
MC1R
Melanocyte
Eumelanin
Pheomelanin

Agouti overexpression (A^y mutation)

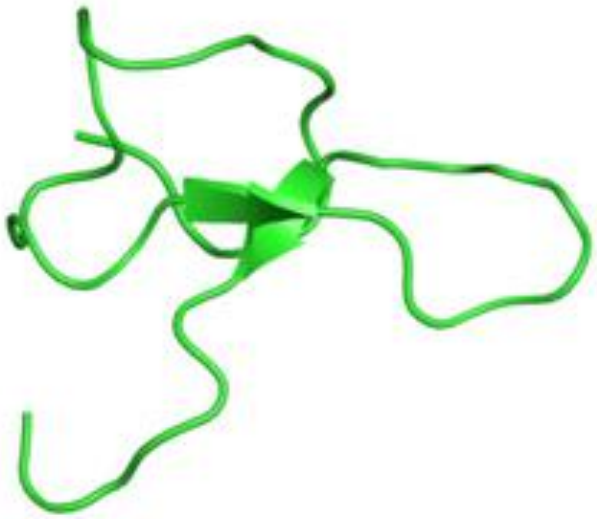


α-MSH = ~~satiety~~ signal



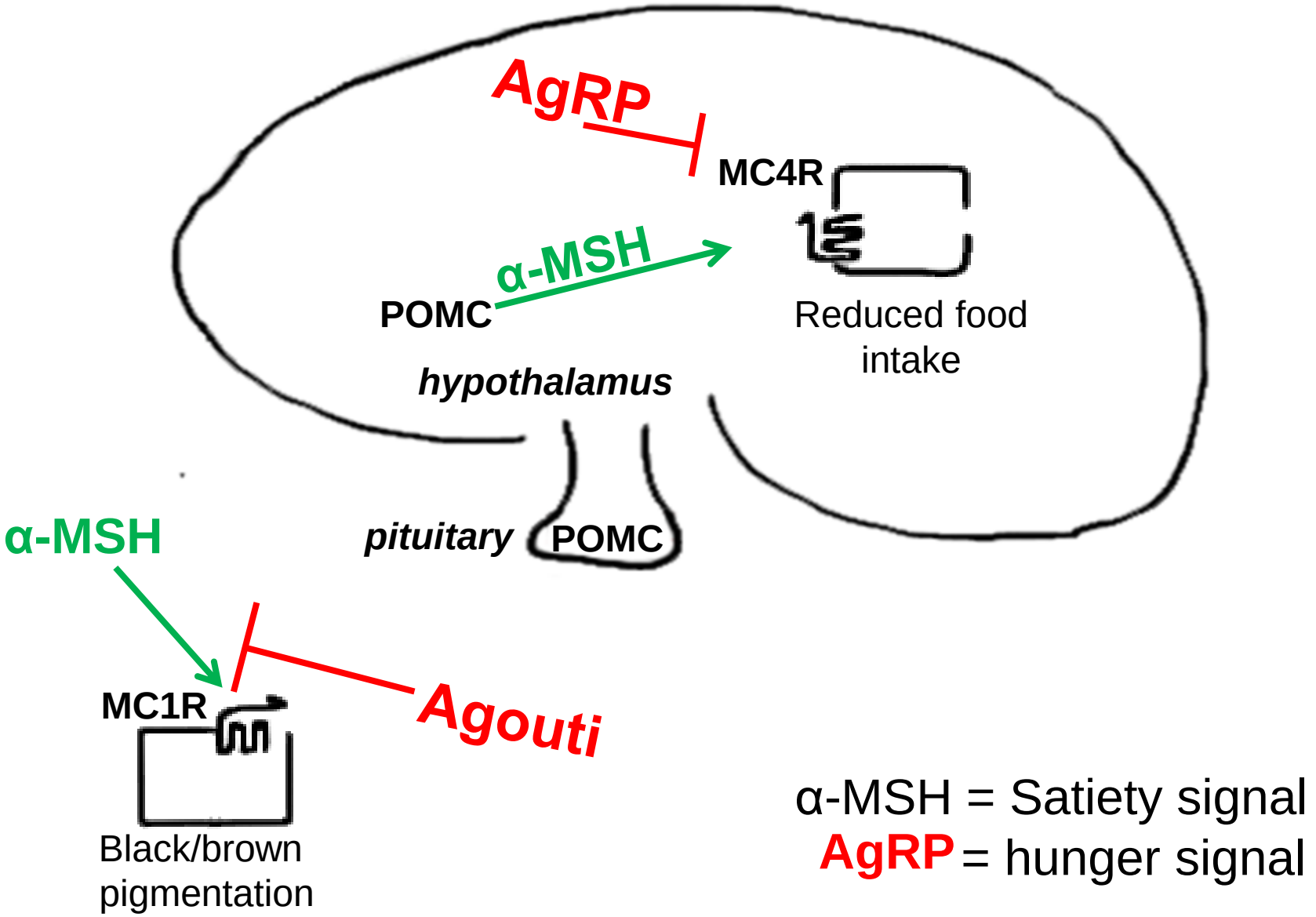
α-MSH = satiety signal

? = hunger signal



Agouti

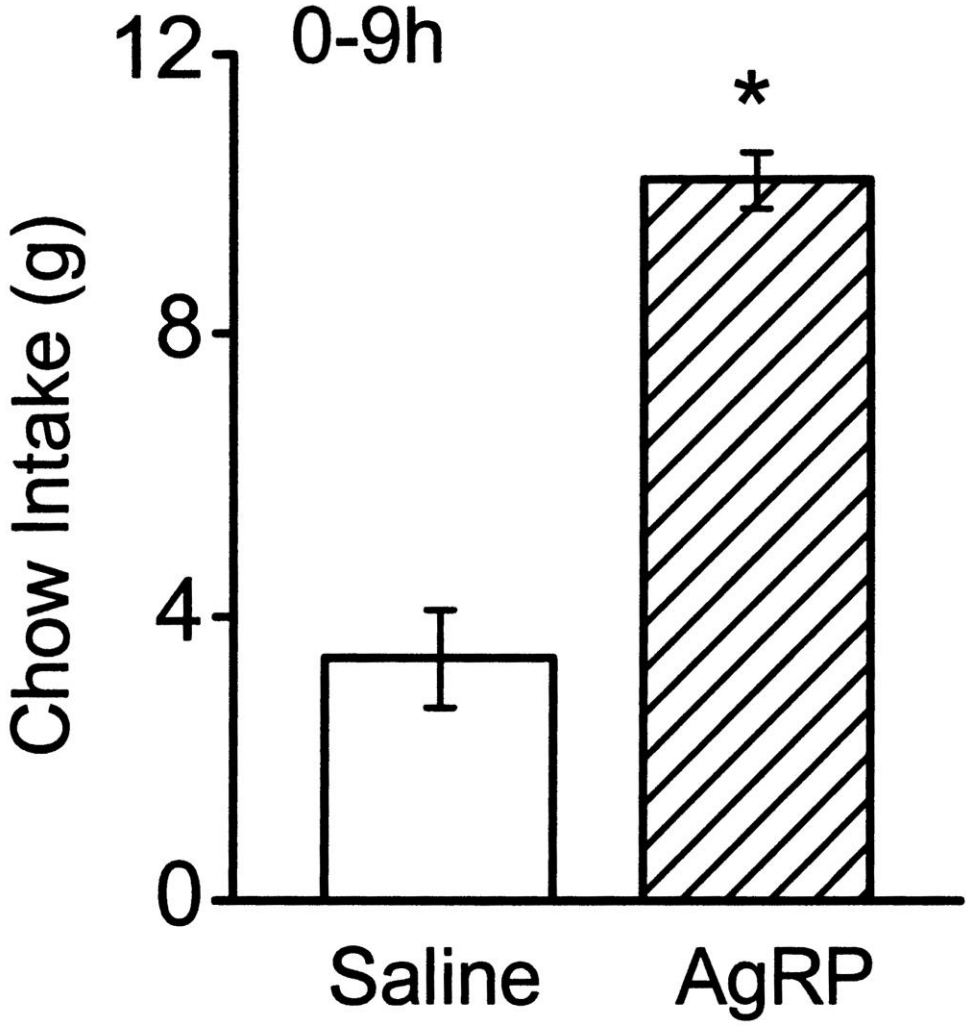
Agouti related protein (AgRP)



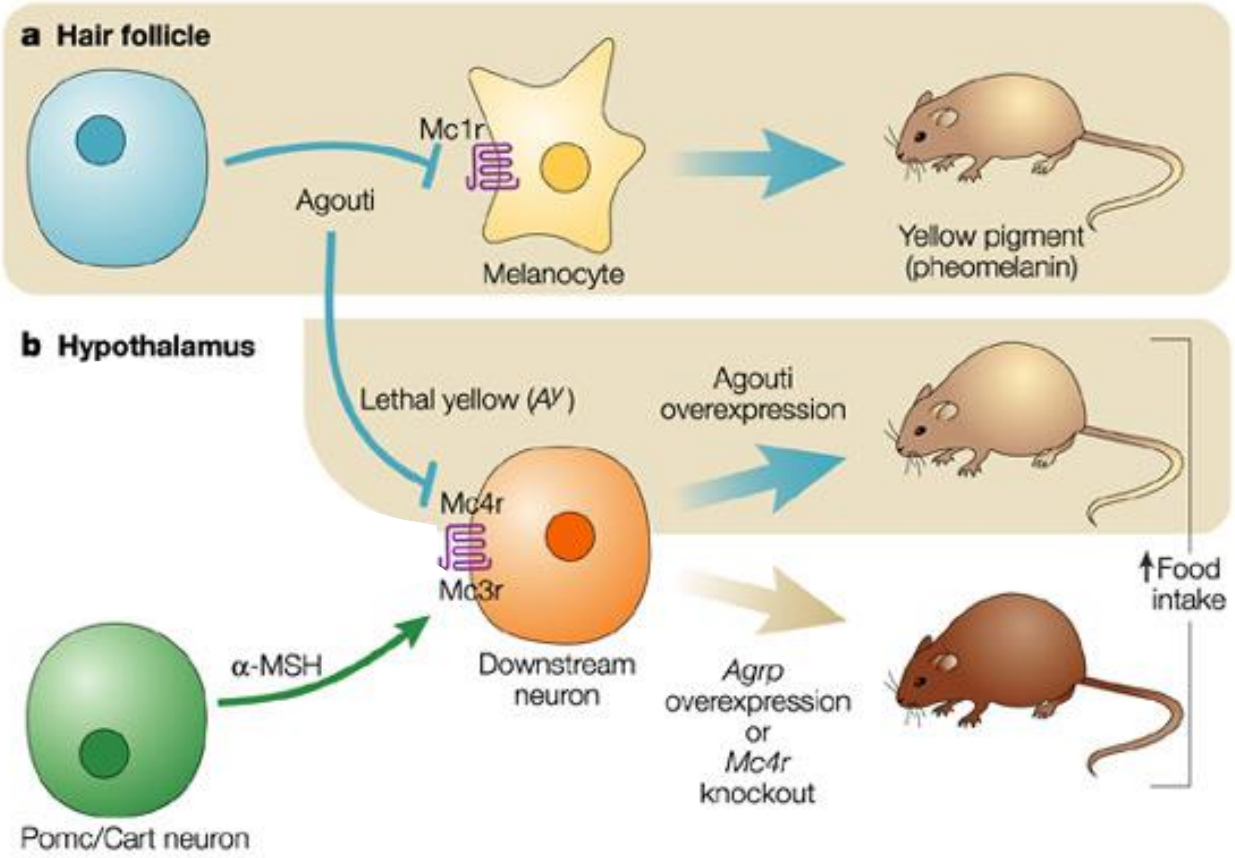
α-MSH = Satiety signal

AgRP = hunger signal

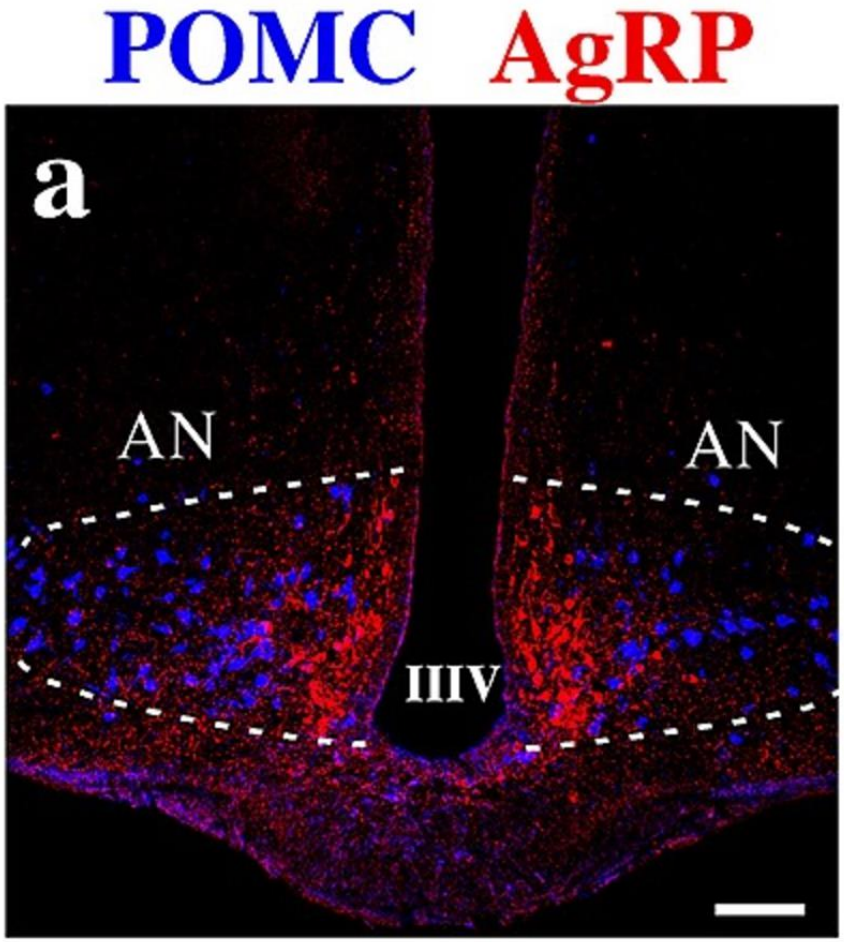
AgRP increases food intake



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

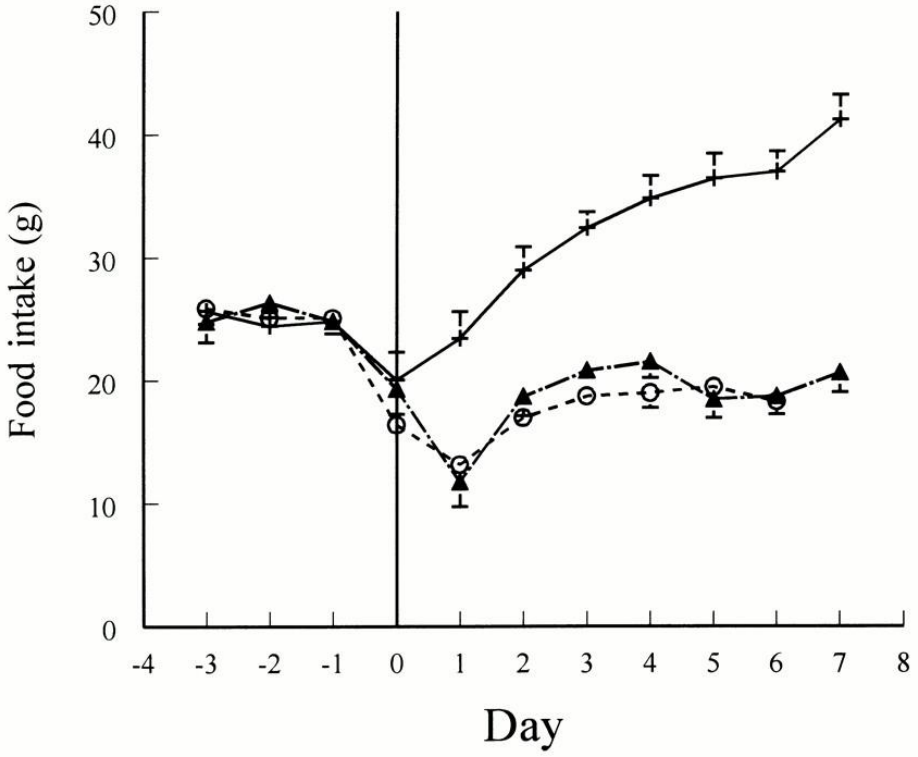


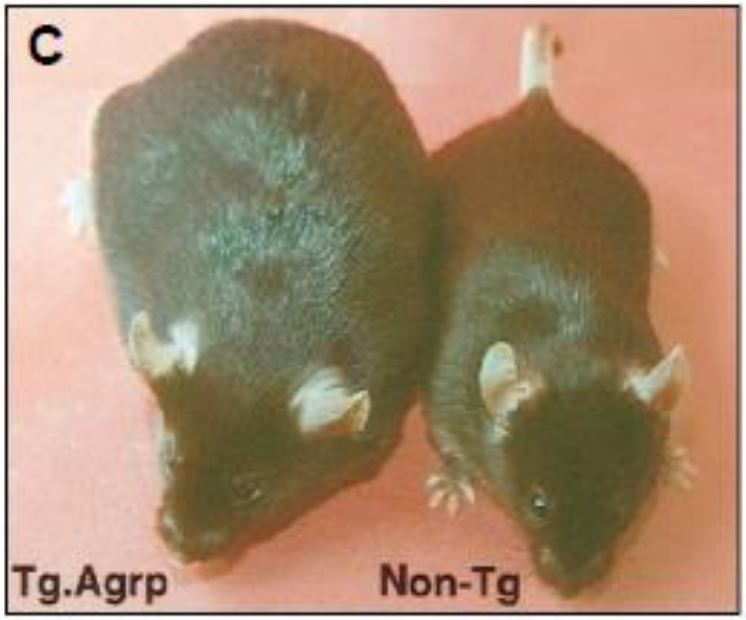
Nature Reviews | Genetics

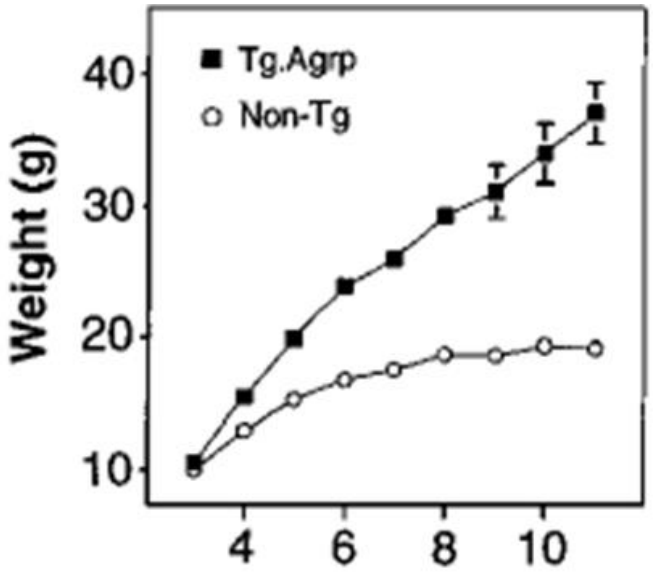


Both AgRP and POMC are localized in the arcuate nucleus (AN) of the hypothalamus.

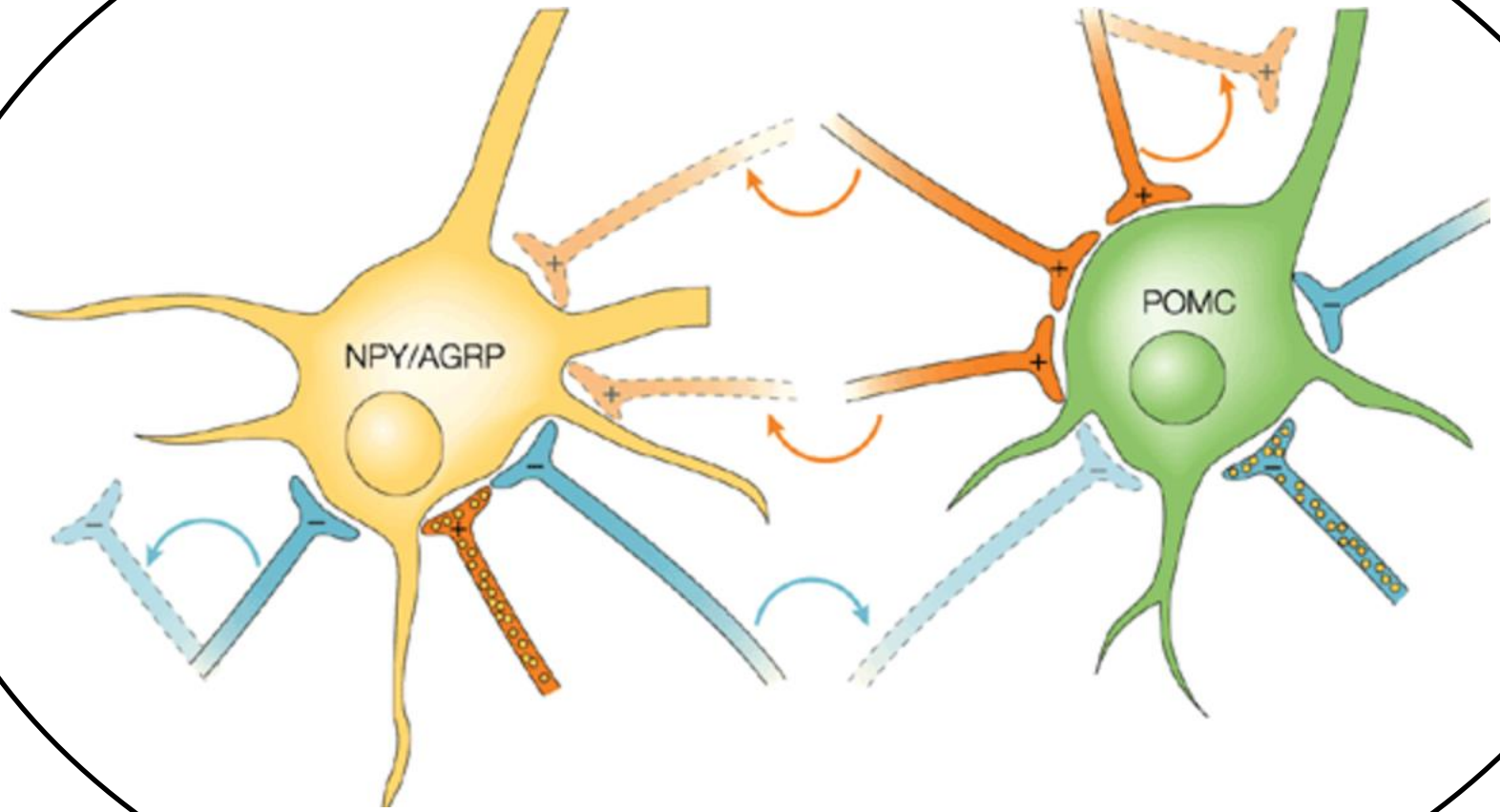
Daily food intake after chronic administration of 1 nmol/day AgRP (83-132) for 7 days.
+, AGRP ad libitum fed group
▲, saline control group.
○, AGRP pair-fed group



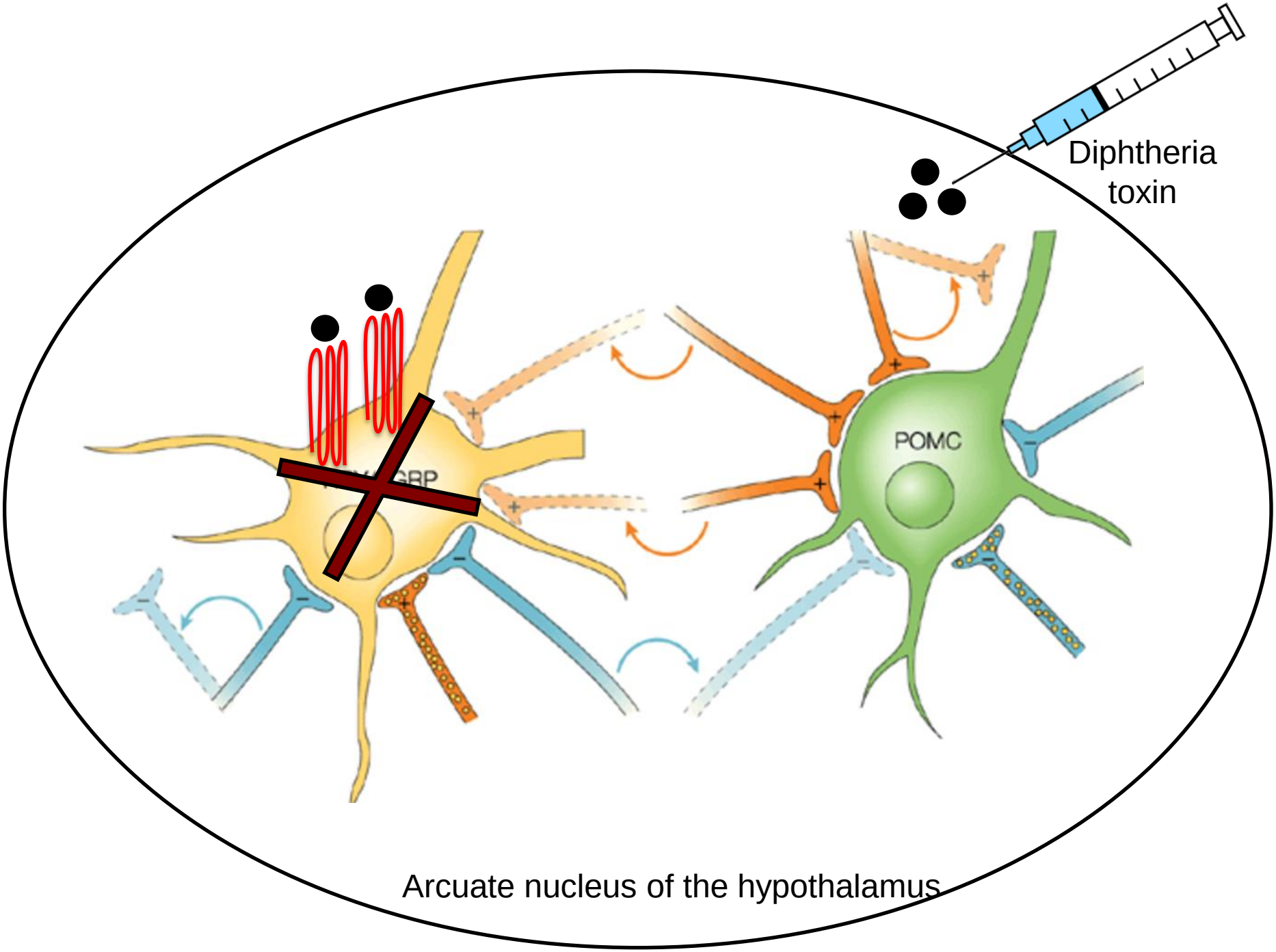


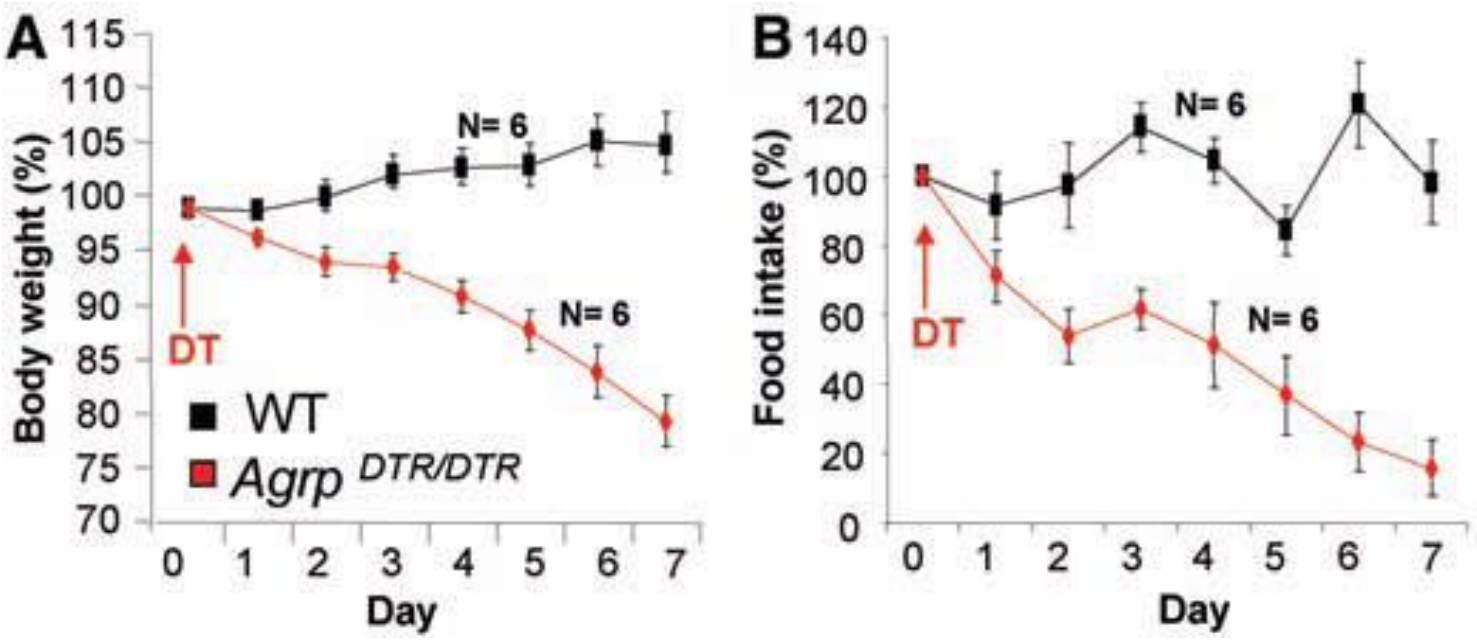


Ollmann et al., 1997

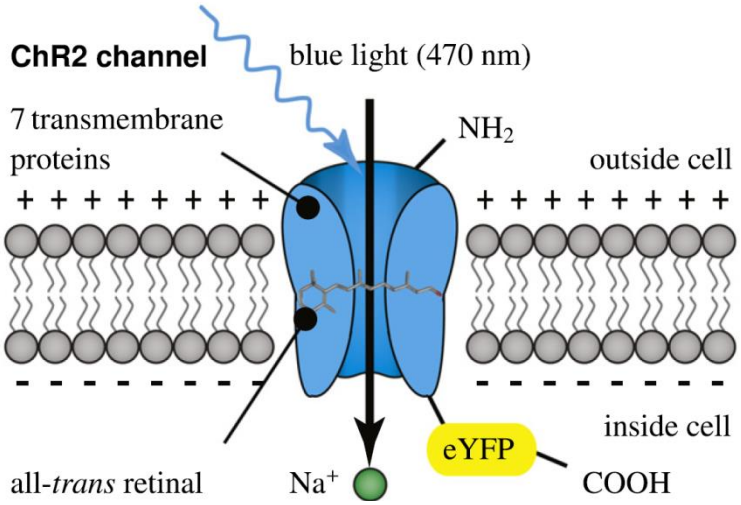


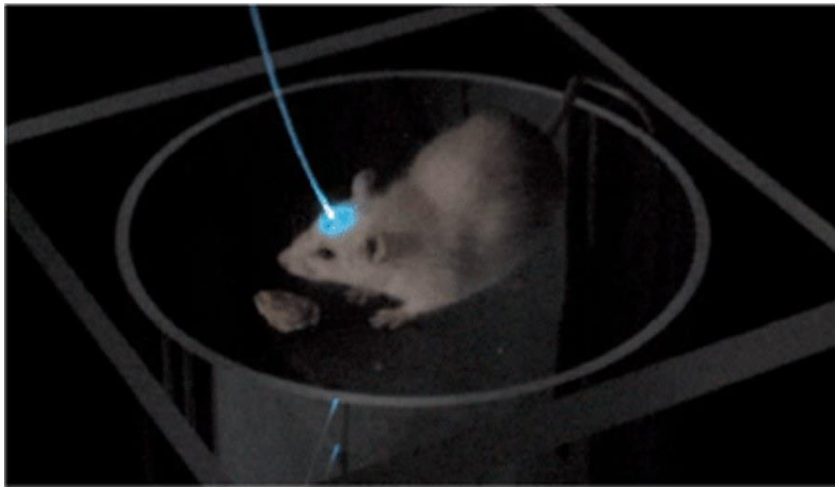
Arcuate nucleus of the hypothalamus


Diphtheria
toxin
POMC
Arcuate nucleus of the hypothalamus

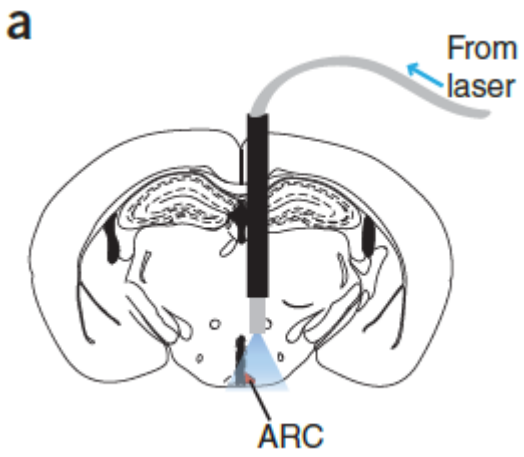


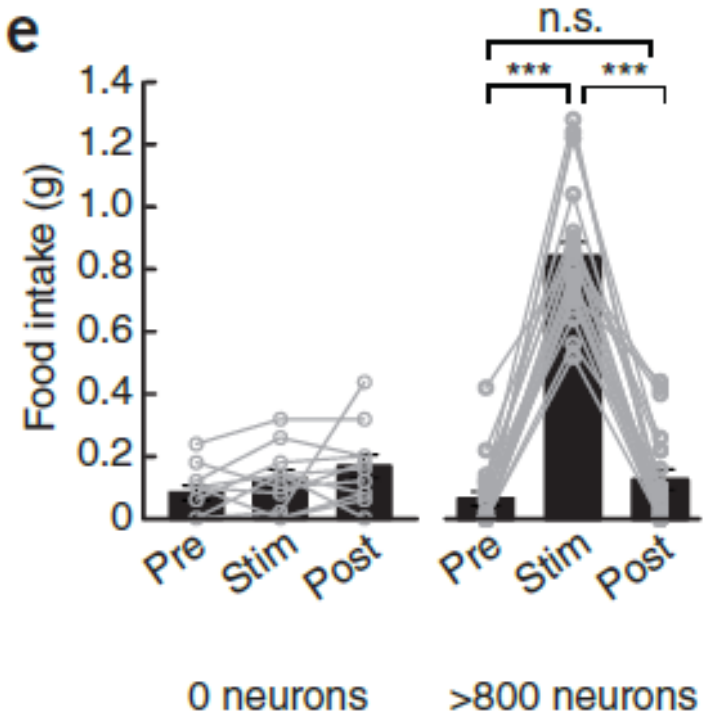
Luque et al. 2005


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



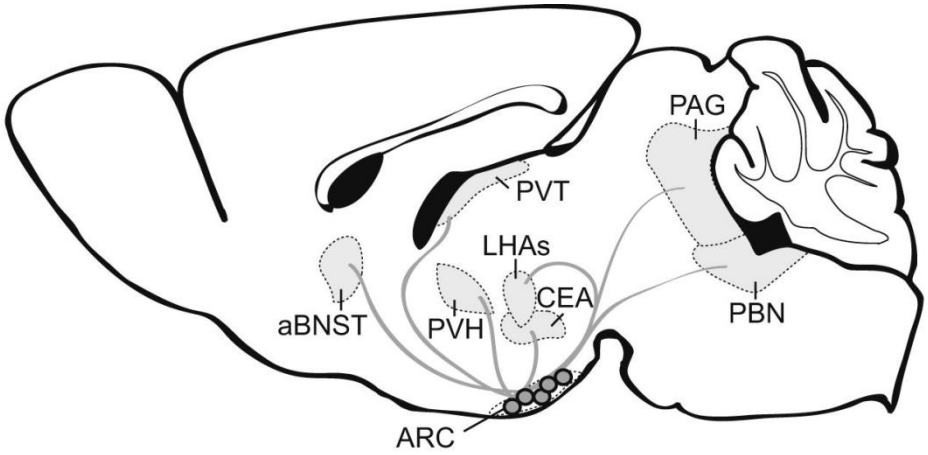
Activation of AgRP neurons leads to binge eating

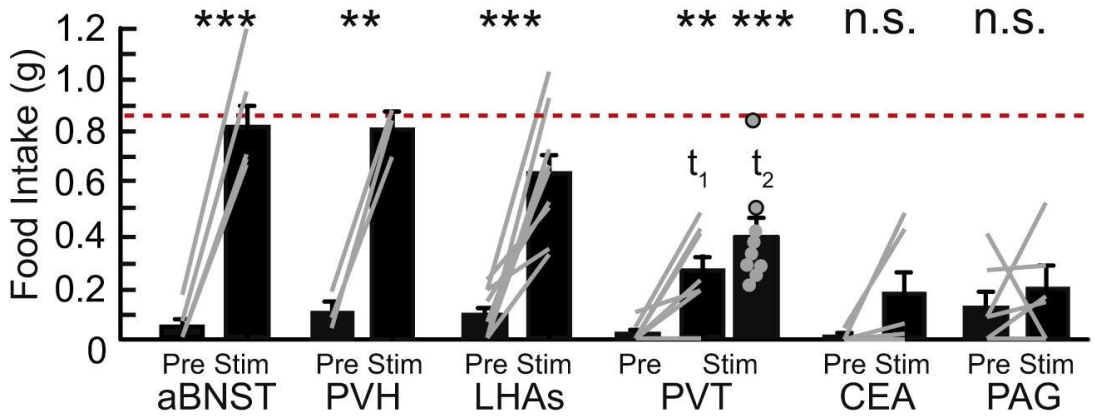




Aponte et al., 2011

AgRP neurocircuitry



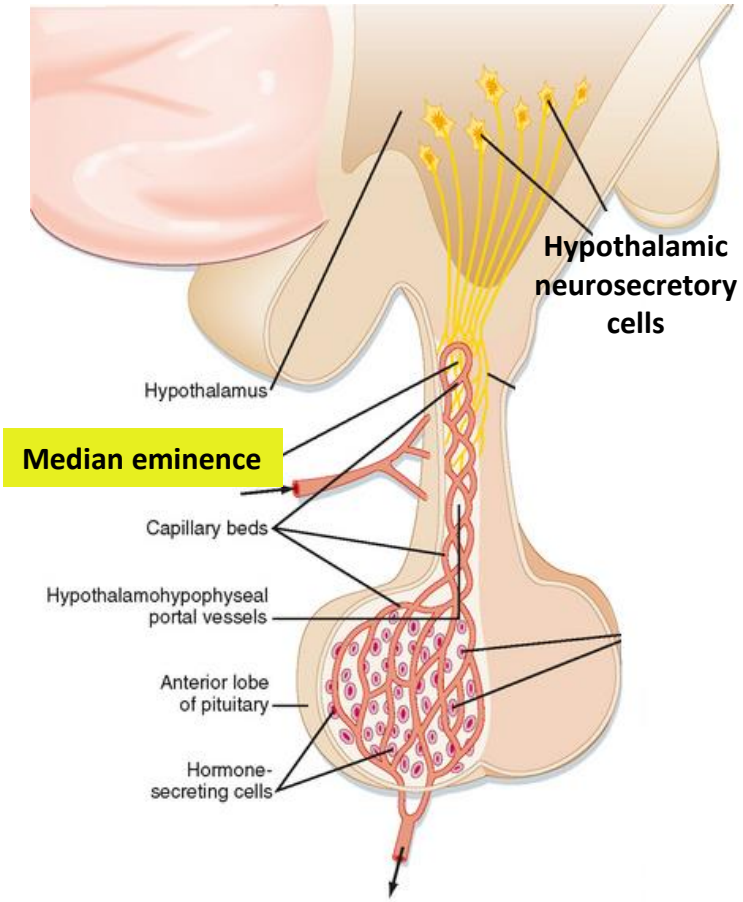


Betley *et al.* 2013

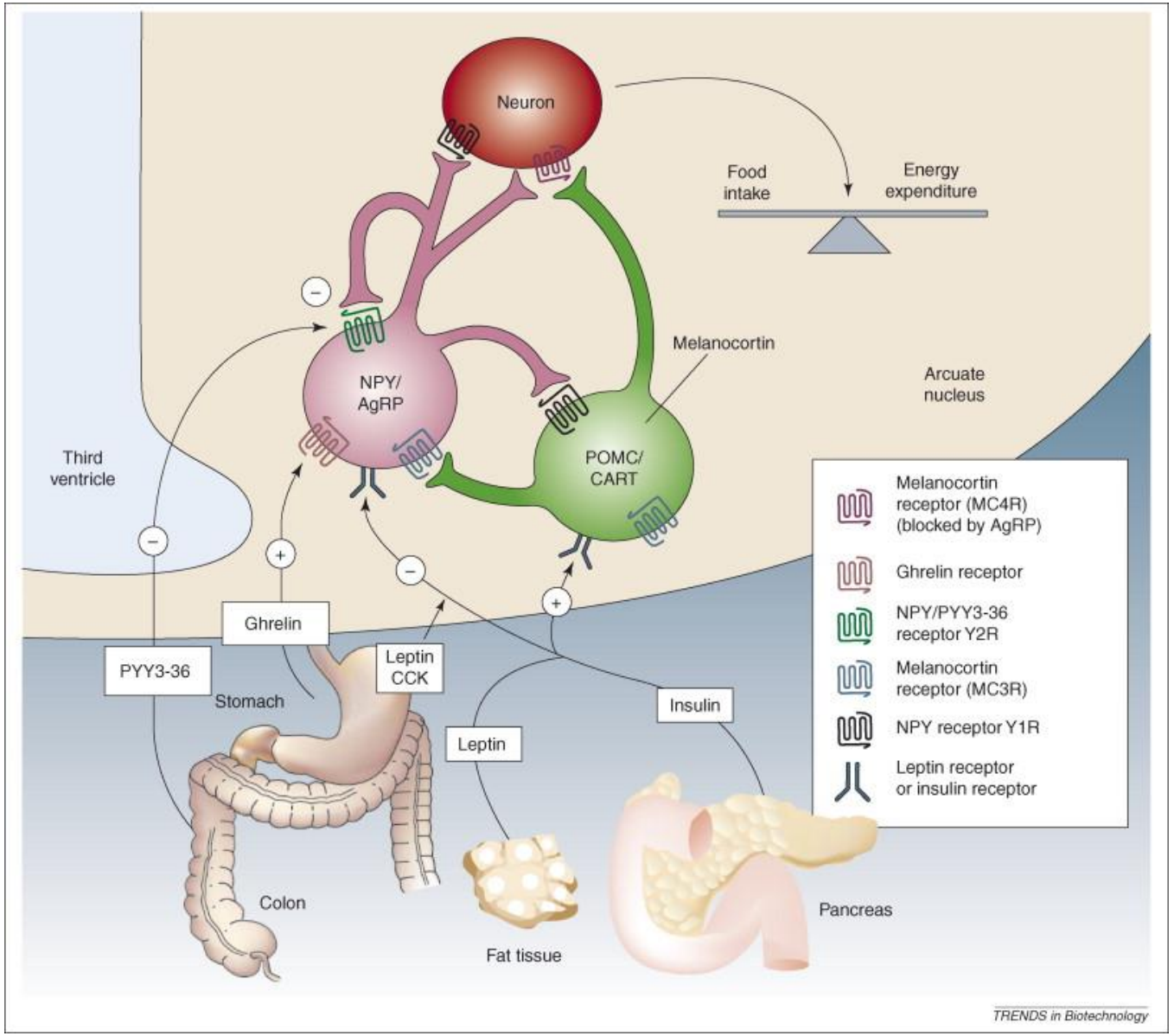
AgRP neurons innervate the pituitary

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

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