Appetite control and the AgRP neuronal system

Yoav Gothilf
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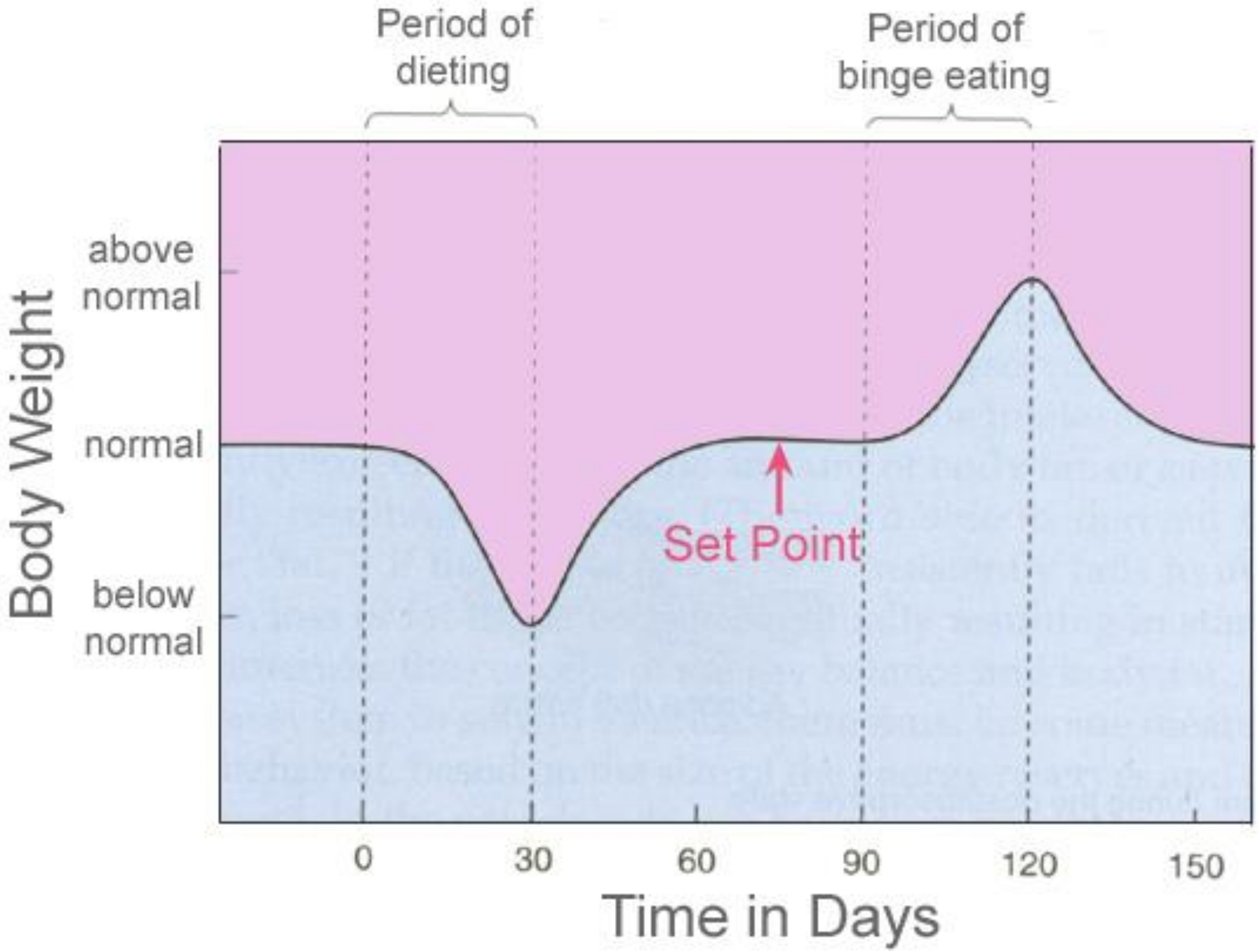
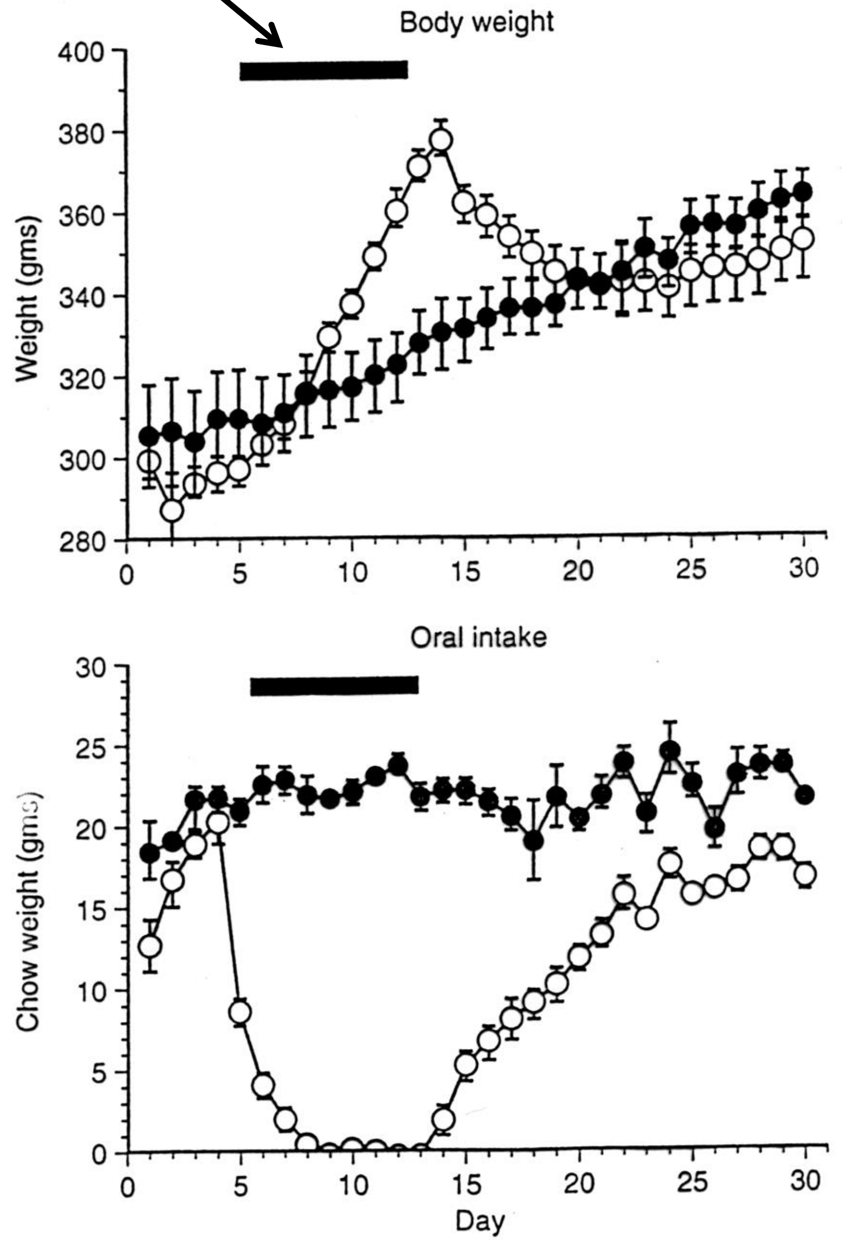
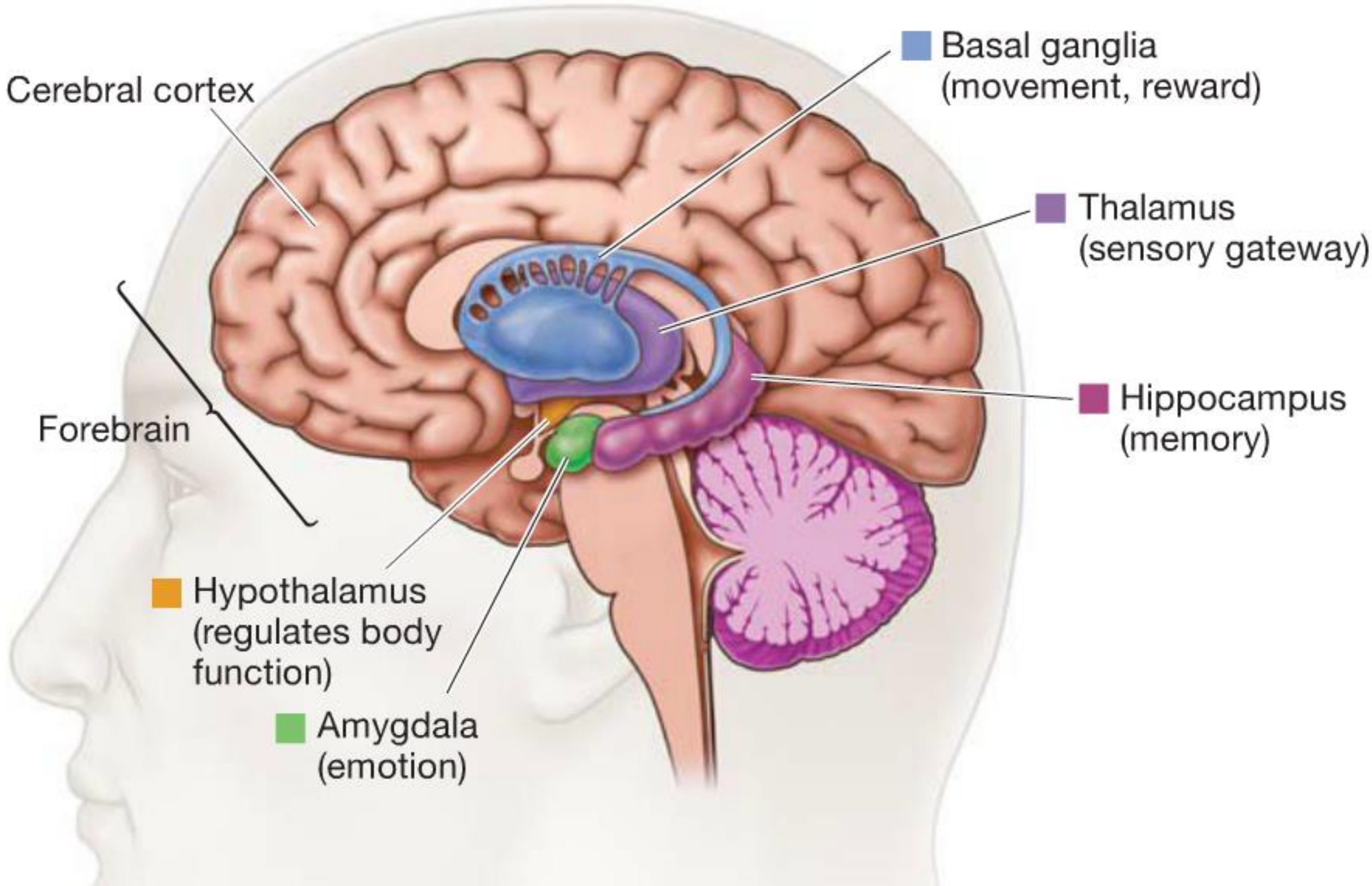


Advantages of keeping steady levels of energy sources.
Not less, not more.

Forced feeding




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

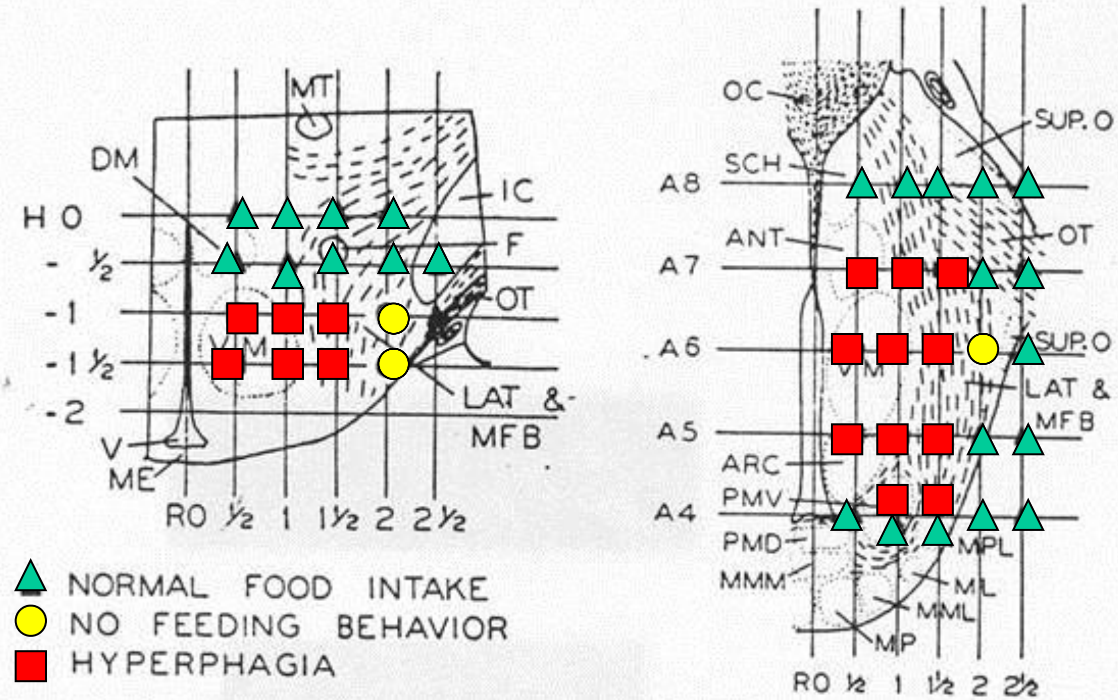
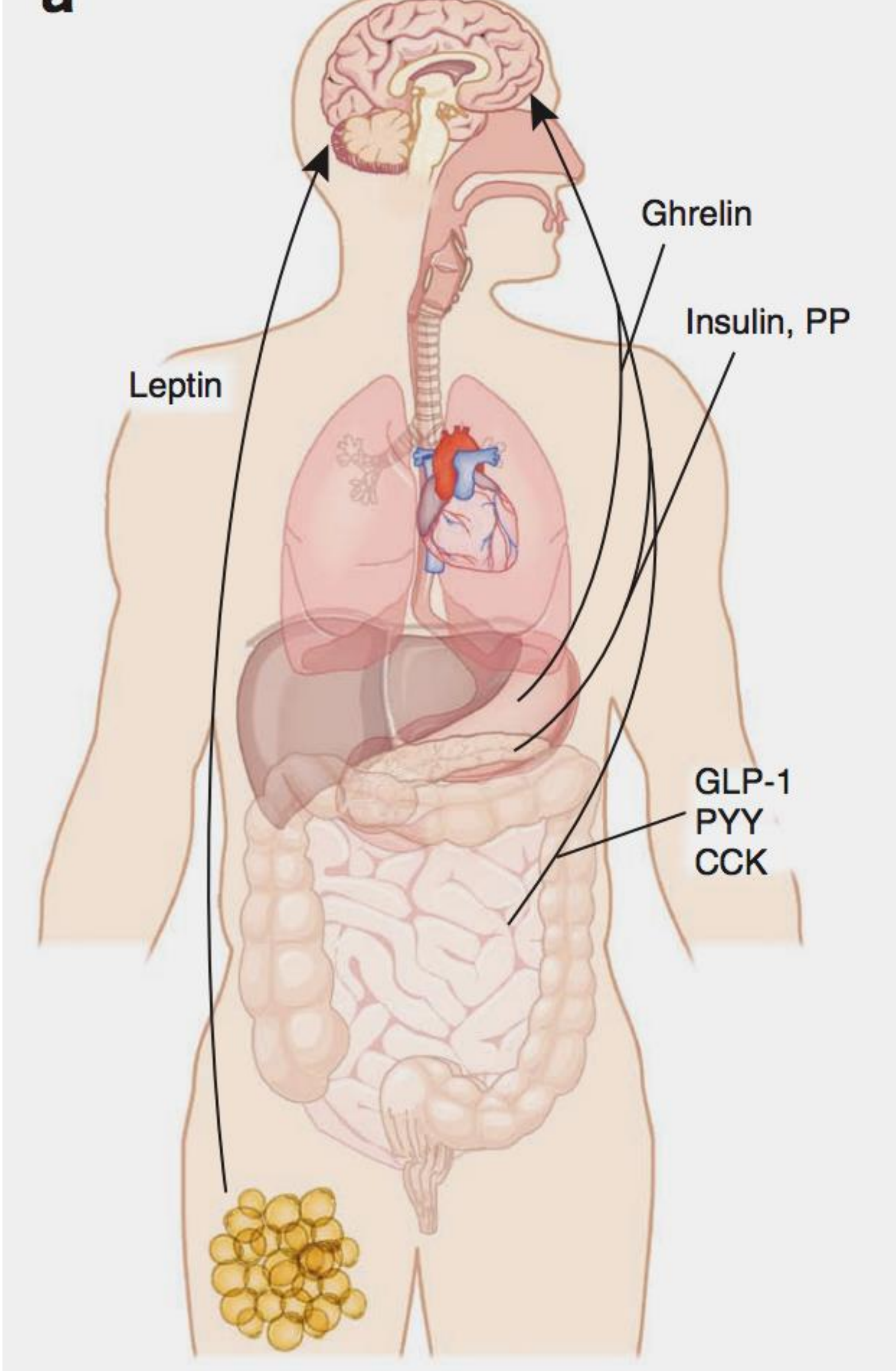


FIGURE 15-4. Cross section of a rat's hypothalmus at level of the ventromedial nucleus (*left*) and of the same side in a horizontal plane, also at the level of the ventromedial nucleus (*right*). Horsley-Clarke coordinates are superimposed. The feeding behavior of rats with small bilaterally symmetrical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

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.

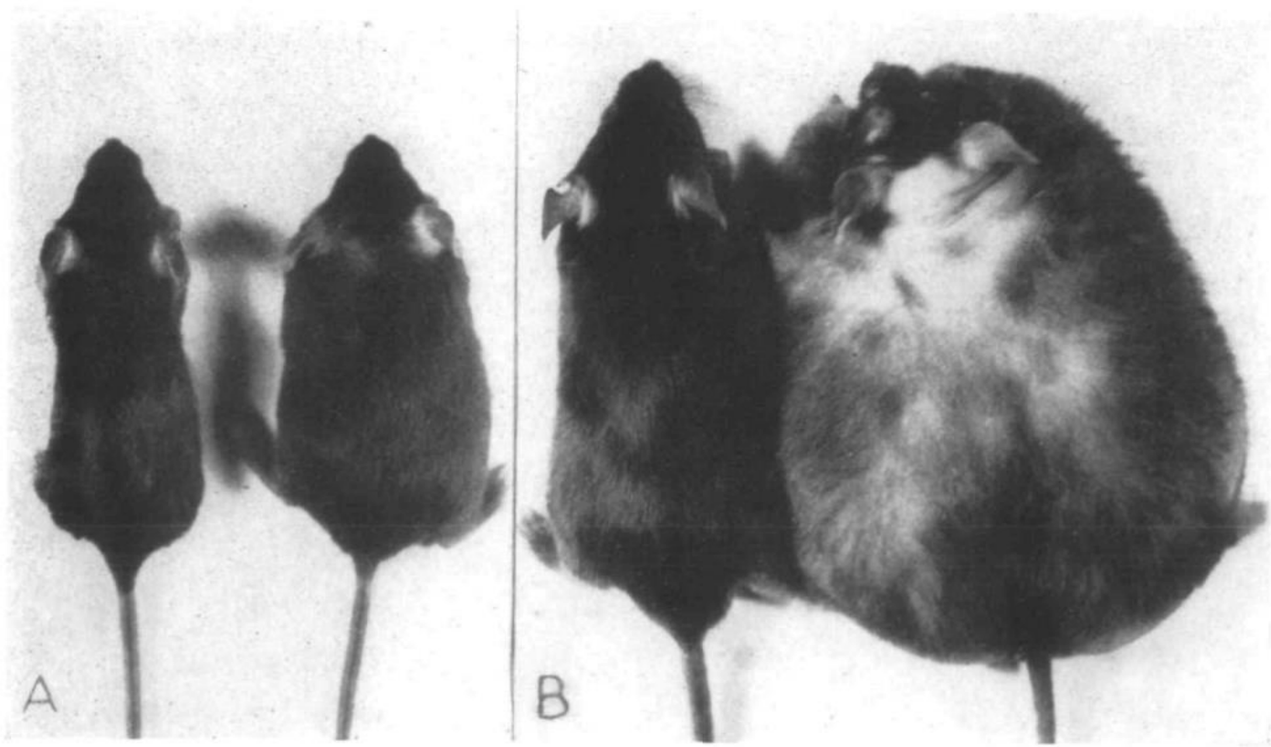
Kennedy, 1953

a



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

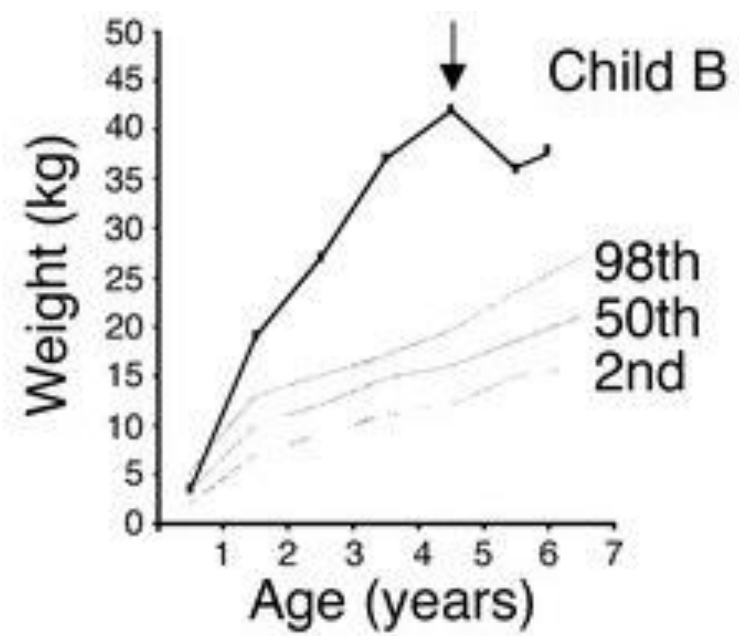
Figure 4

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 and mild diabetes

J Hered (1950)

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.

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*‡

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† These authors contributed equally to this study.

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

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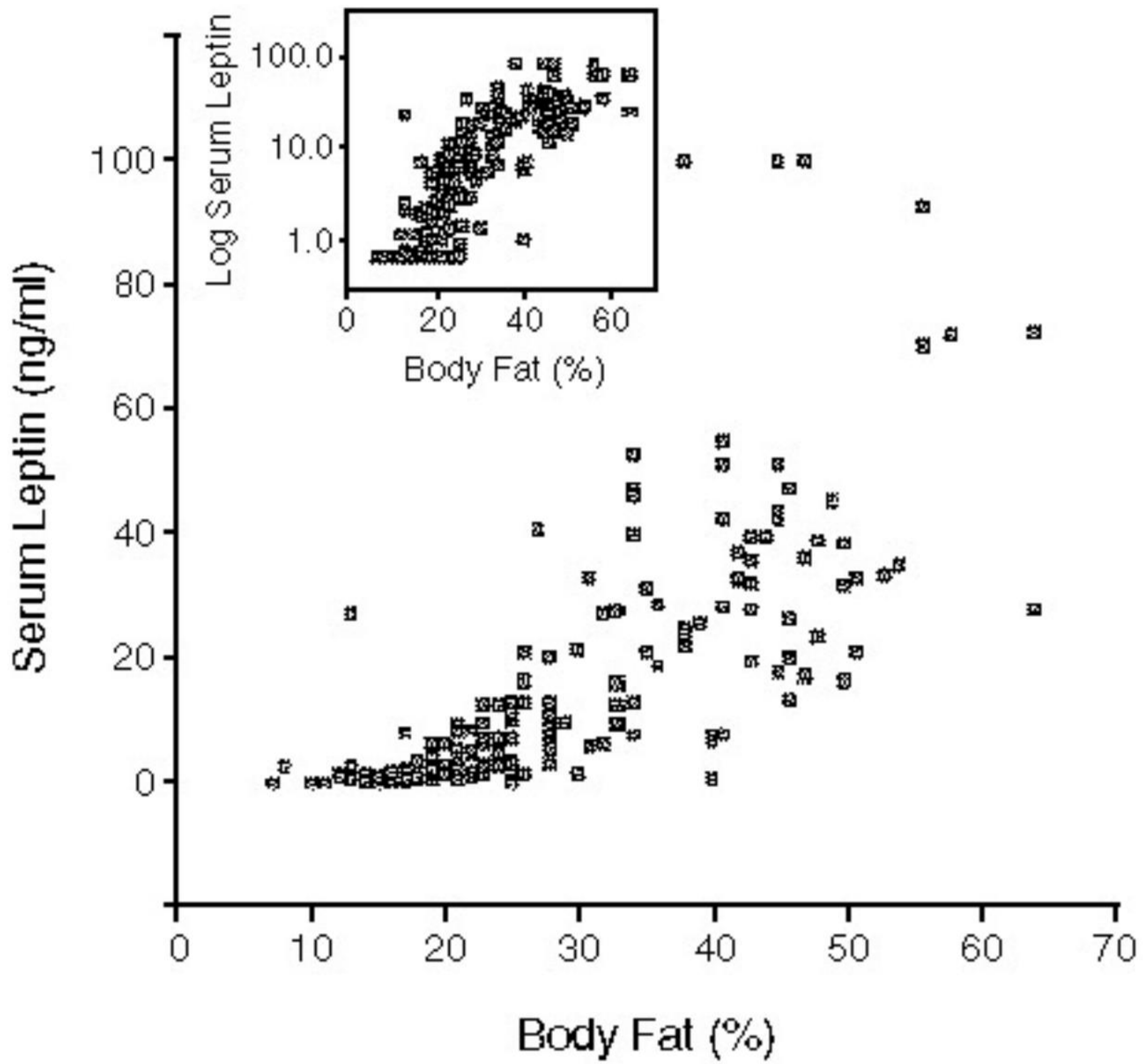
‖ Explorations fonctionnelles endocriniennes, Hôpital d'enfant Armand Trousseau, avenue du Dr Arnold Netter, 75012 Paris, France

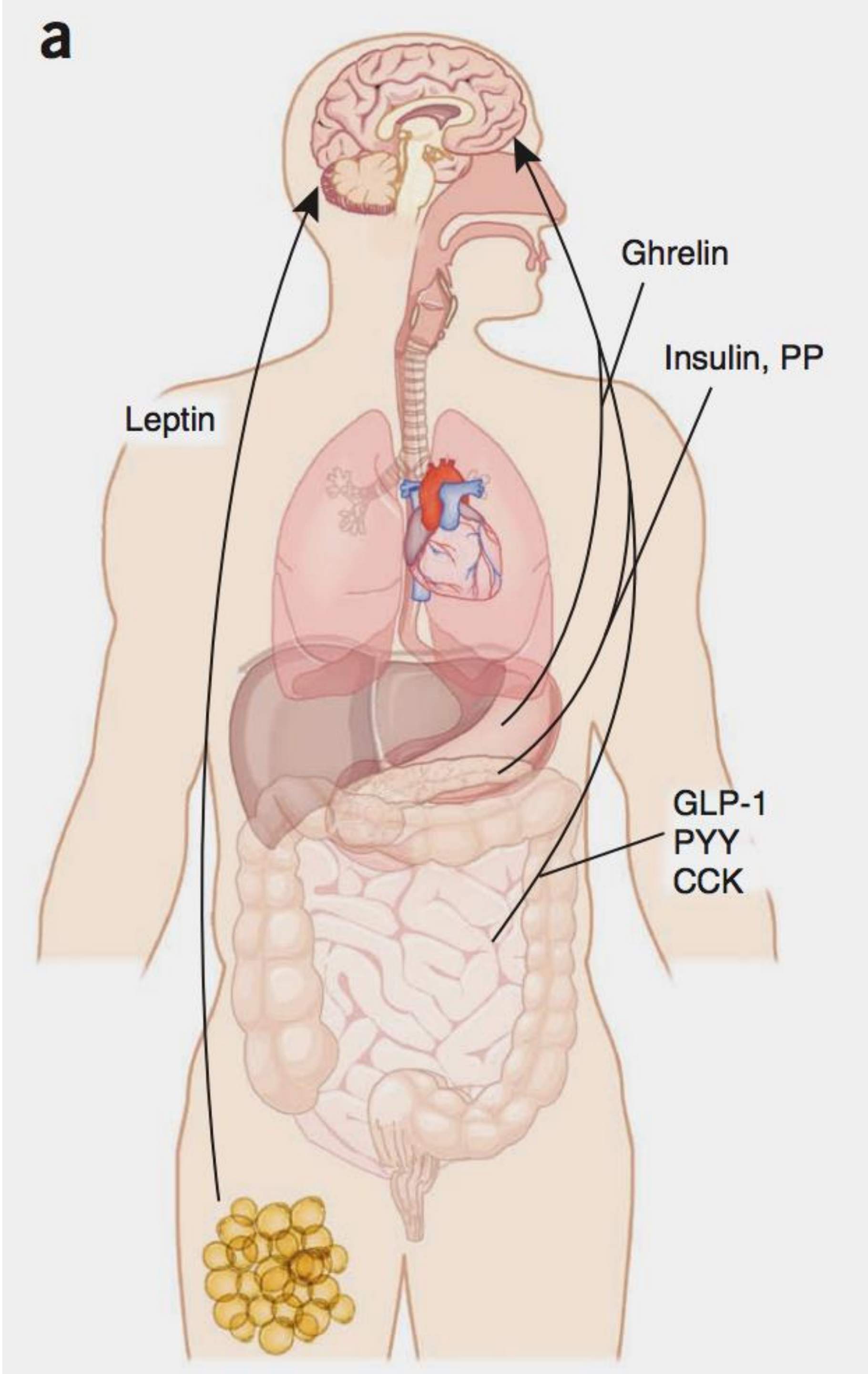
¶ CJF INSERM 9508, 15 rue de l'Ecole de Médecine, 75005 Paris, France

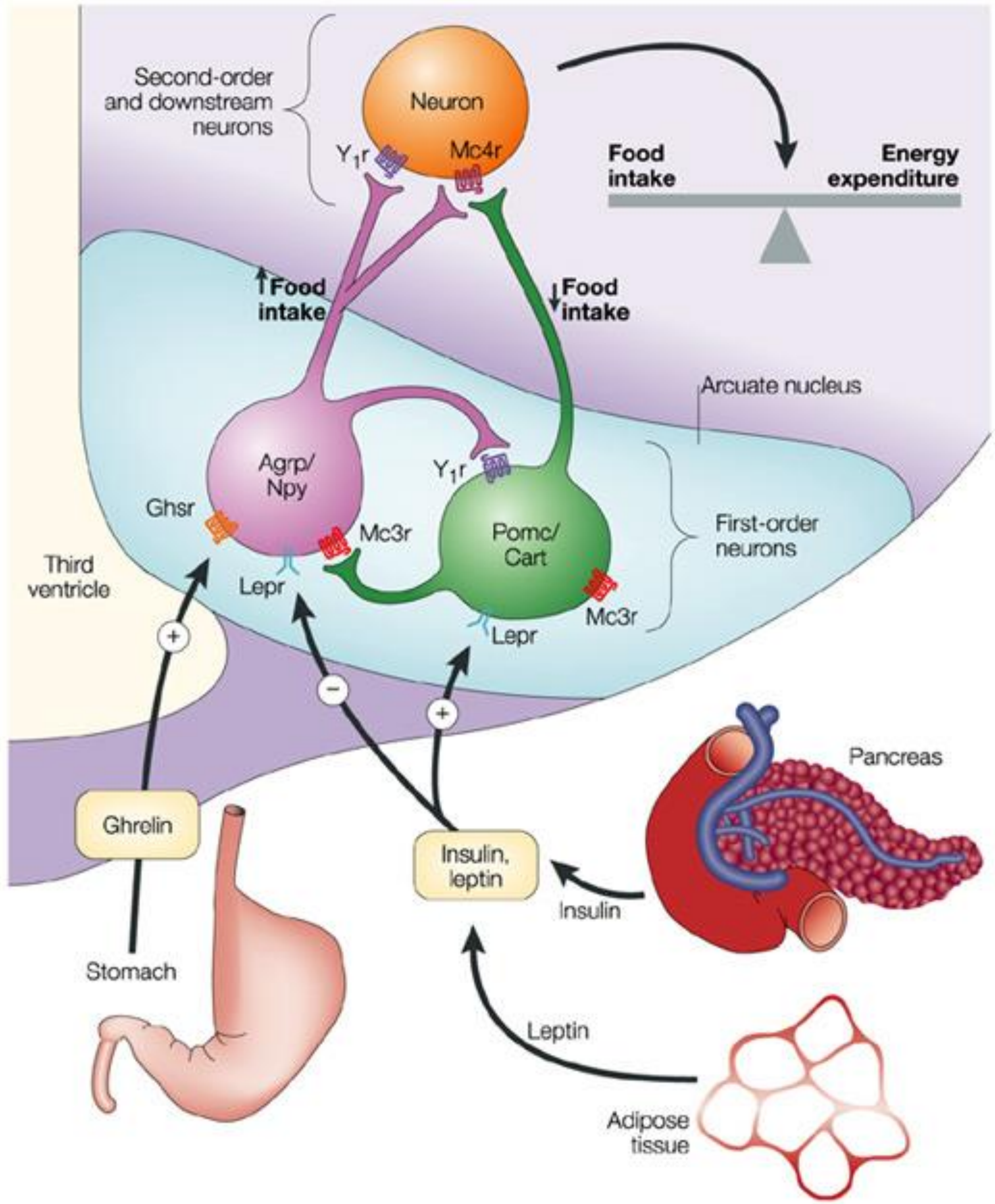
‡ These authors contributed equally to this work.

Blood Leptin concentration correlates with body weight

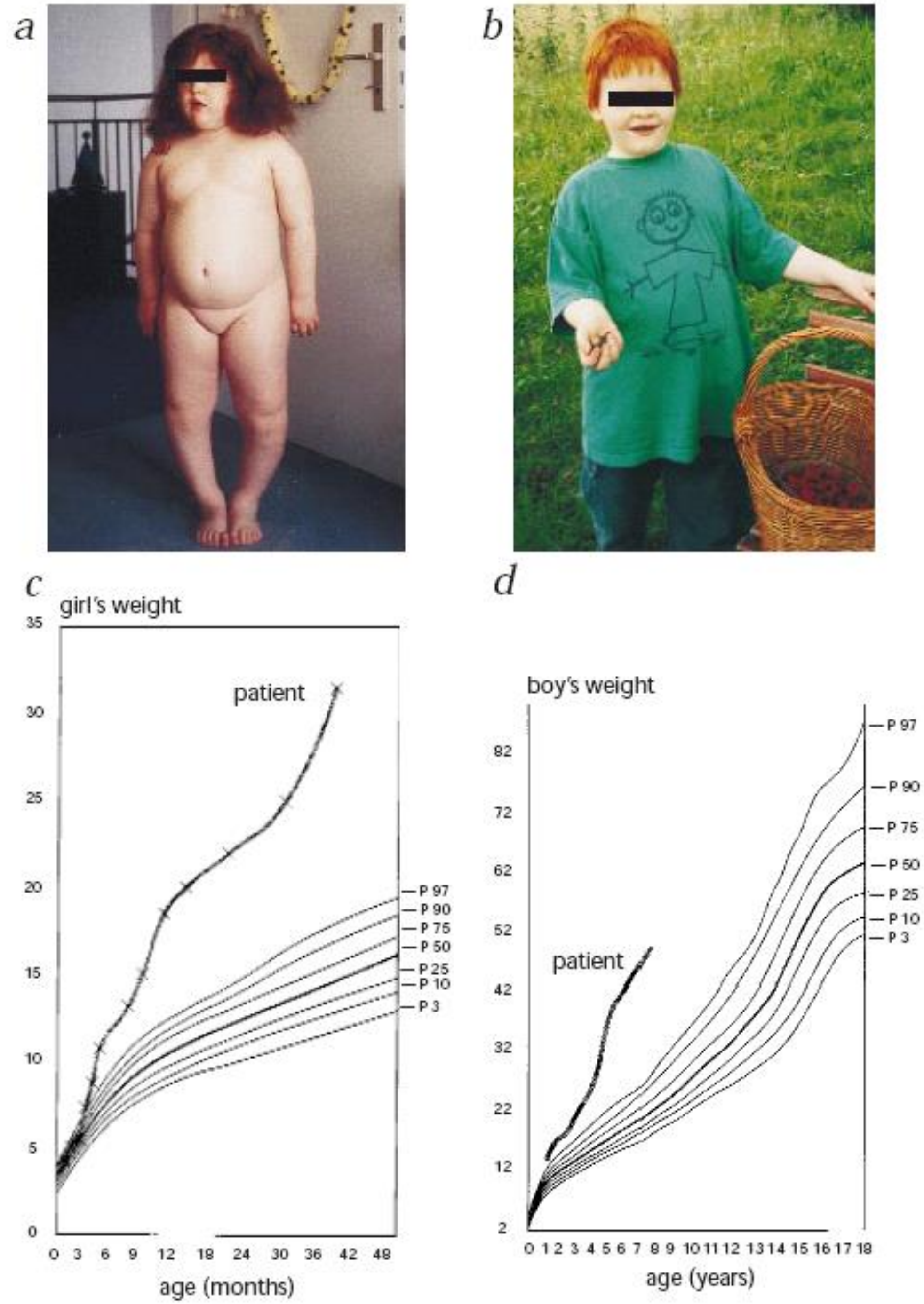


N Engl J Med 1996; 334:292-295


a
Ghrelin
Insulin, PP
Leptin
GLP-1
PYY
CCK



Nature Reviews | Genetics



Krude et al., 1998

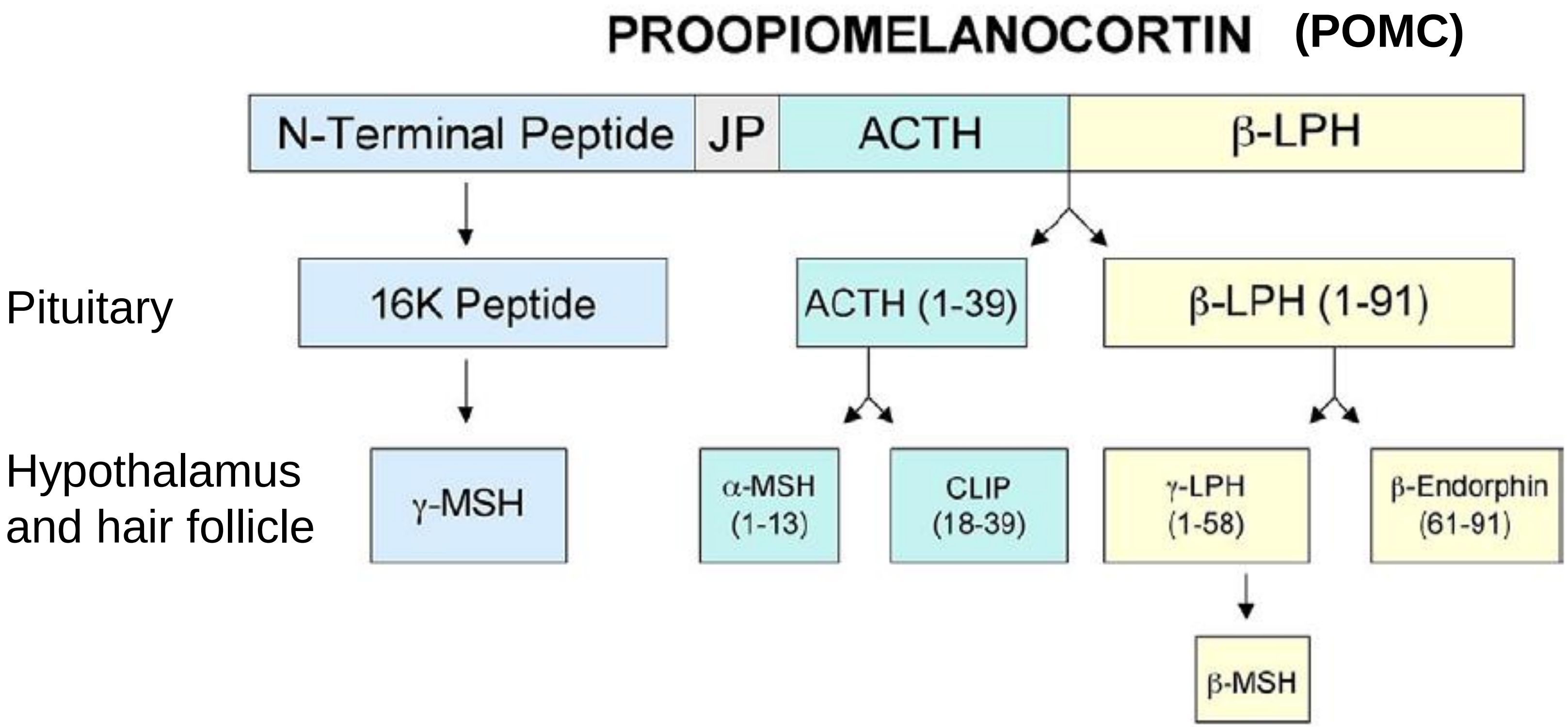
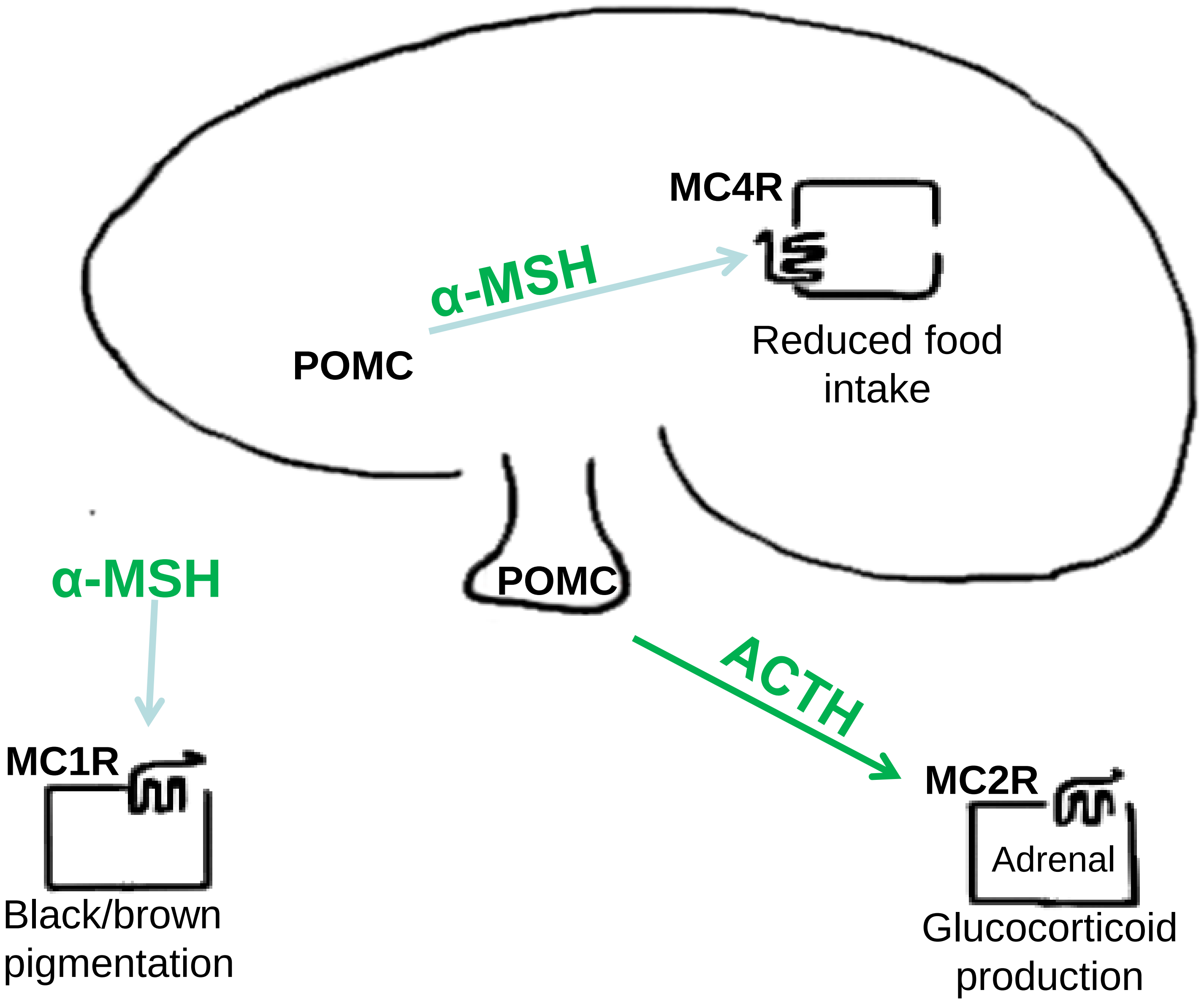
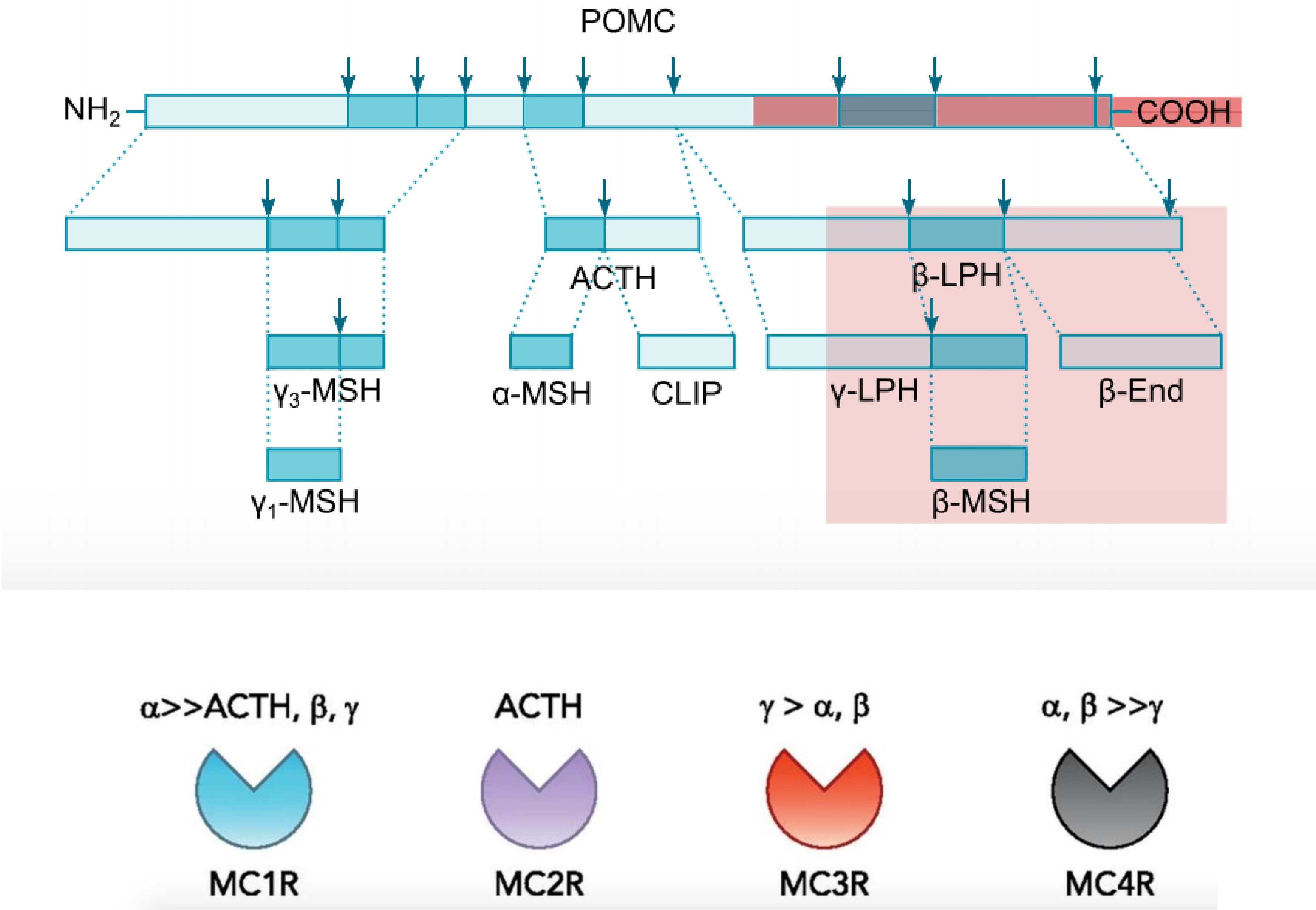


Figure 2. Schematic diagram of the POMC precursor molecule and the major peptide products which are derived from this precursor by endoproteolytic cleavage. (JP = Joining peptide; LPH= Lipotropin; CLIP= corticotropin-like-intermediate lobe peptide).

POMC functions in stress response, pigmentation and food consumption

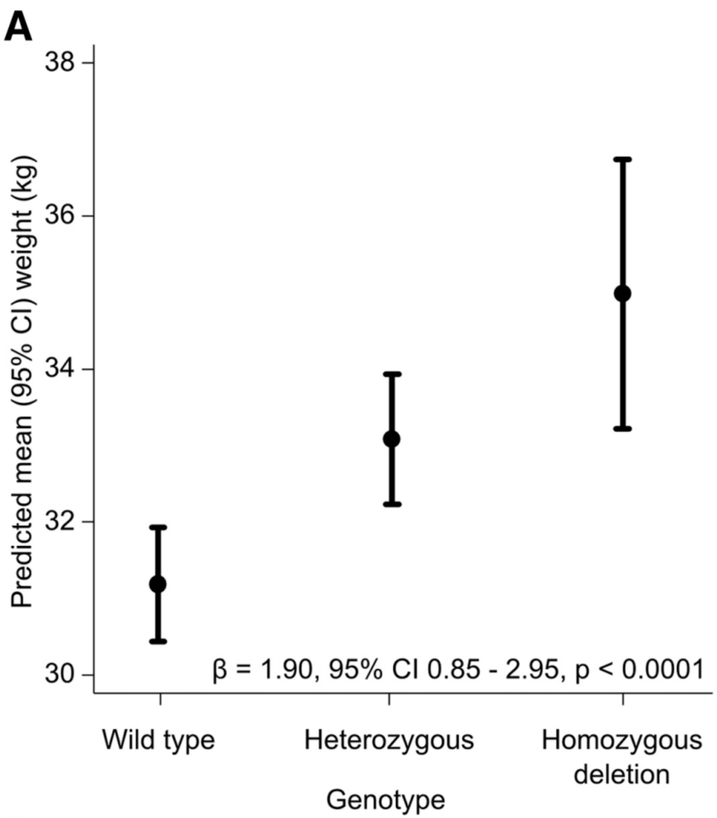


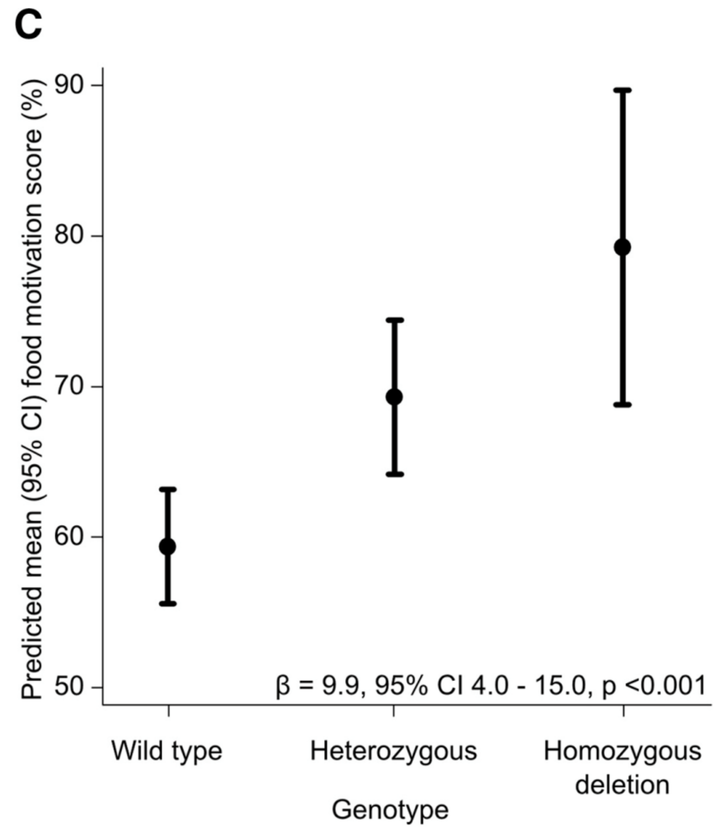


Raffan et al. 2016 *Cell Metabolism*

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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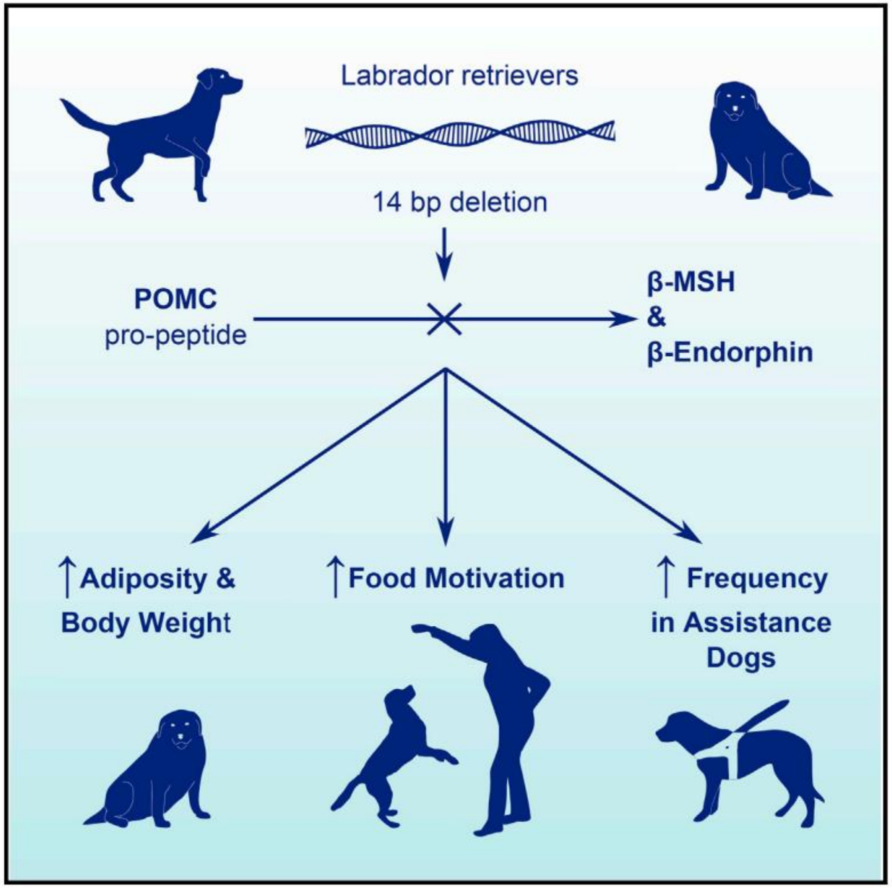
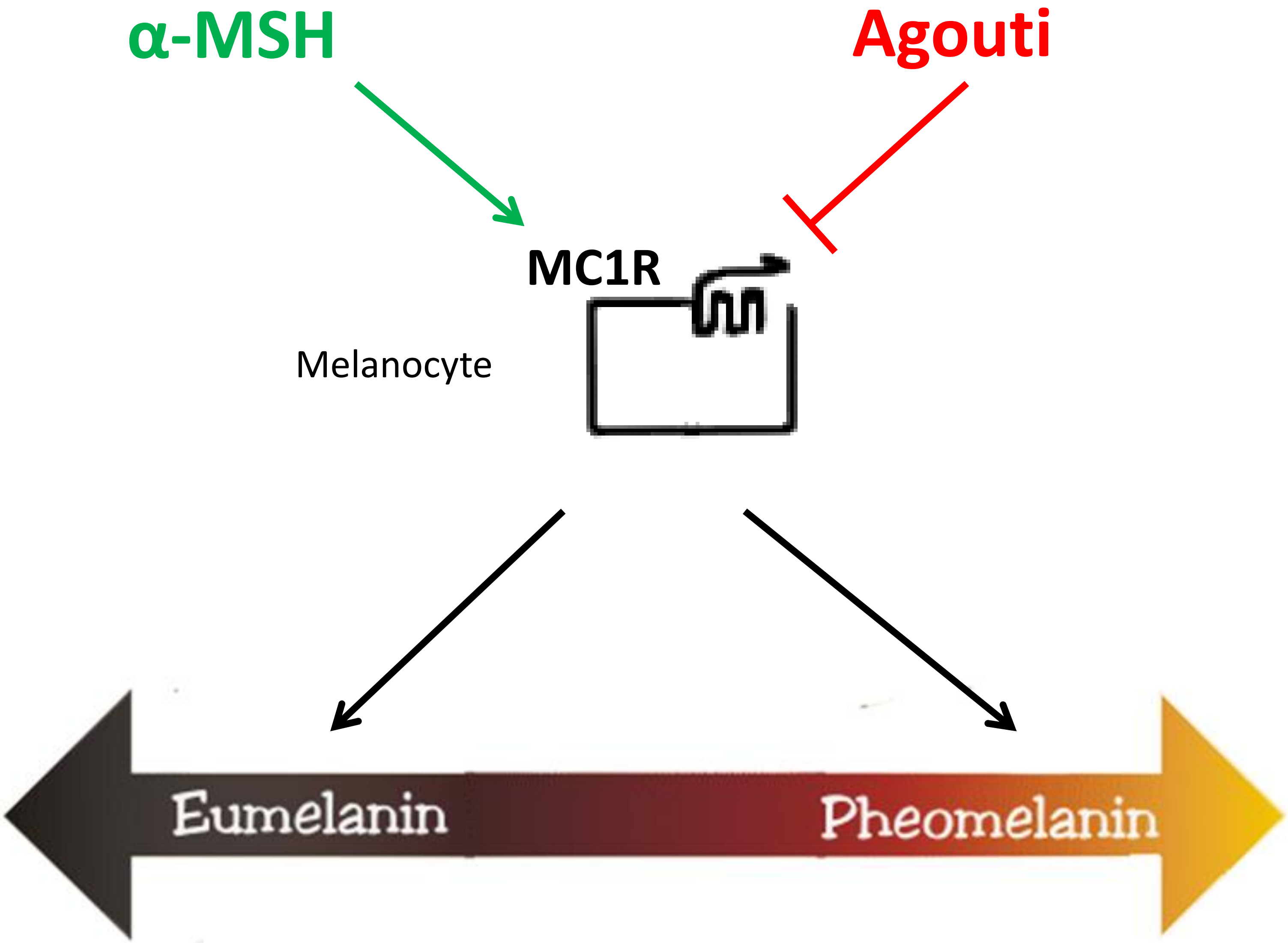
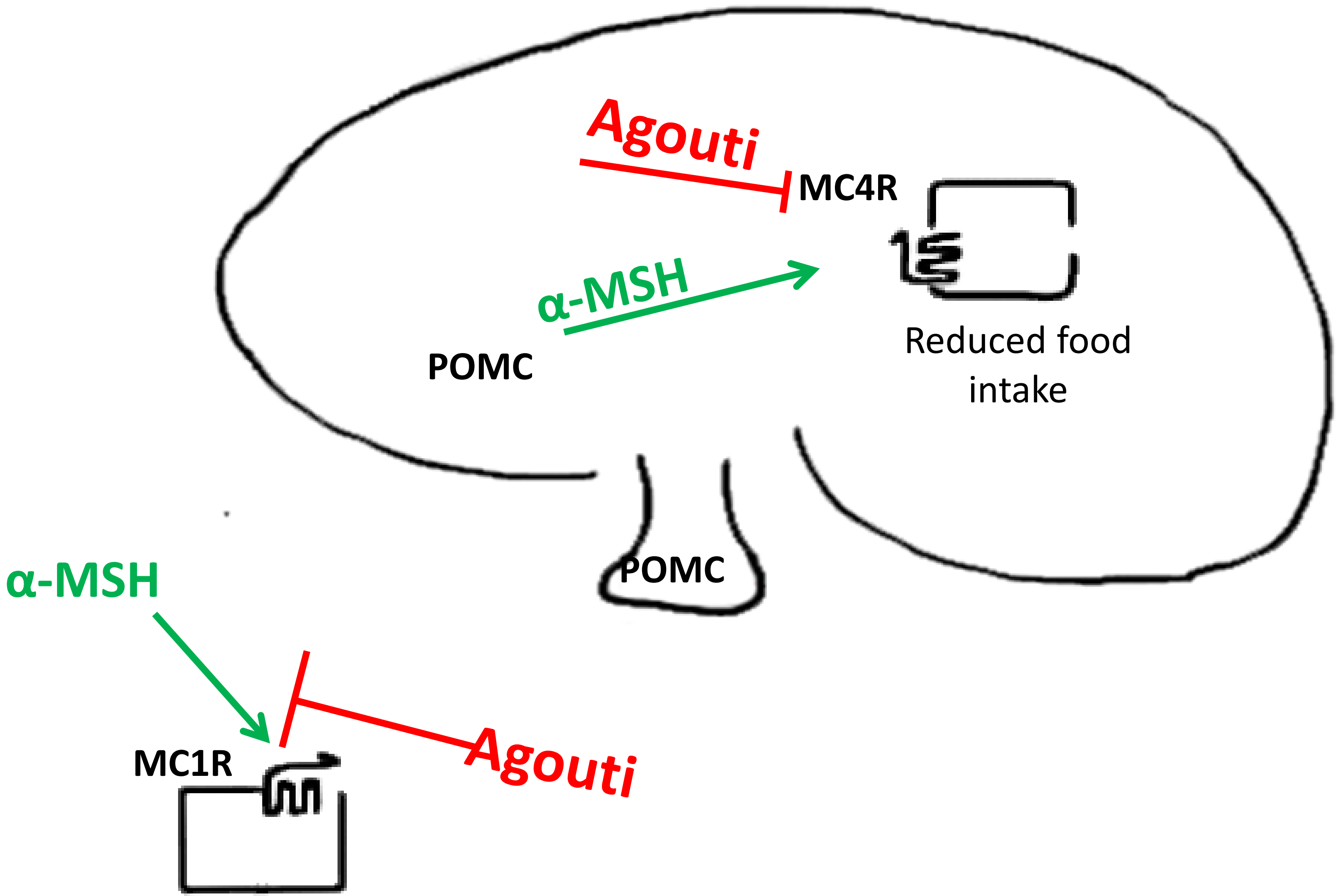


http://www.cam.ac.uk/research/news/genetic-variant-may-help-explain-why-labradors-are-prone-to-obesity

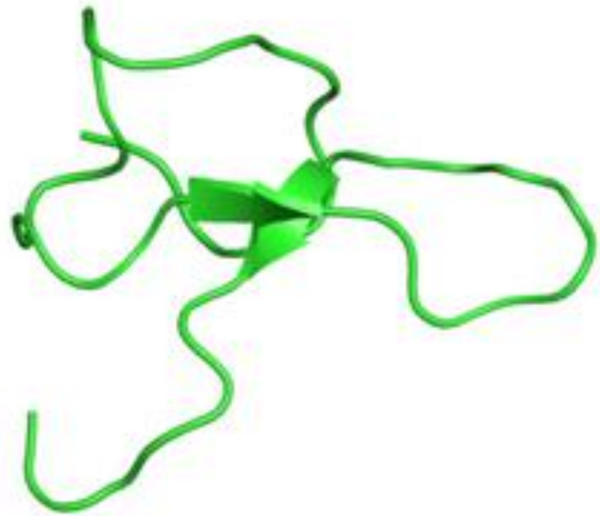
A^y mutation


α-MSH
Agouti
MC1R
Melanocyte
Eumelanin
Pheomelanin

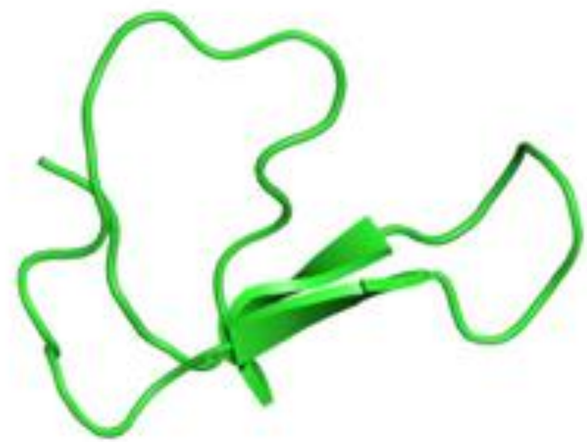
Agouti overexpression (A^y mutation)



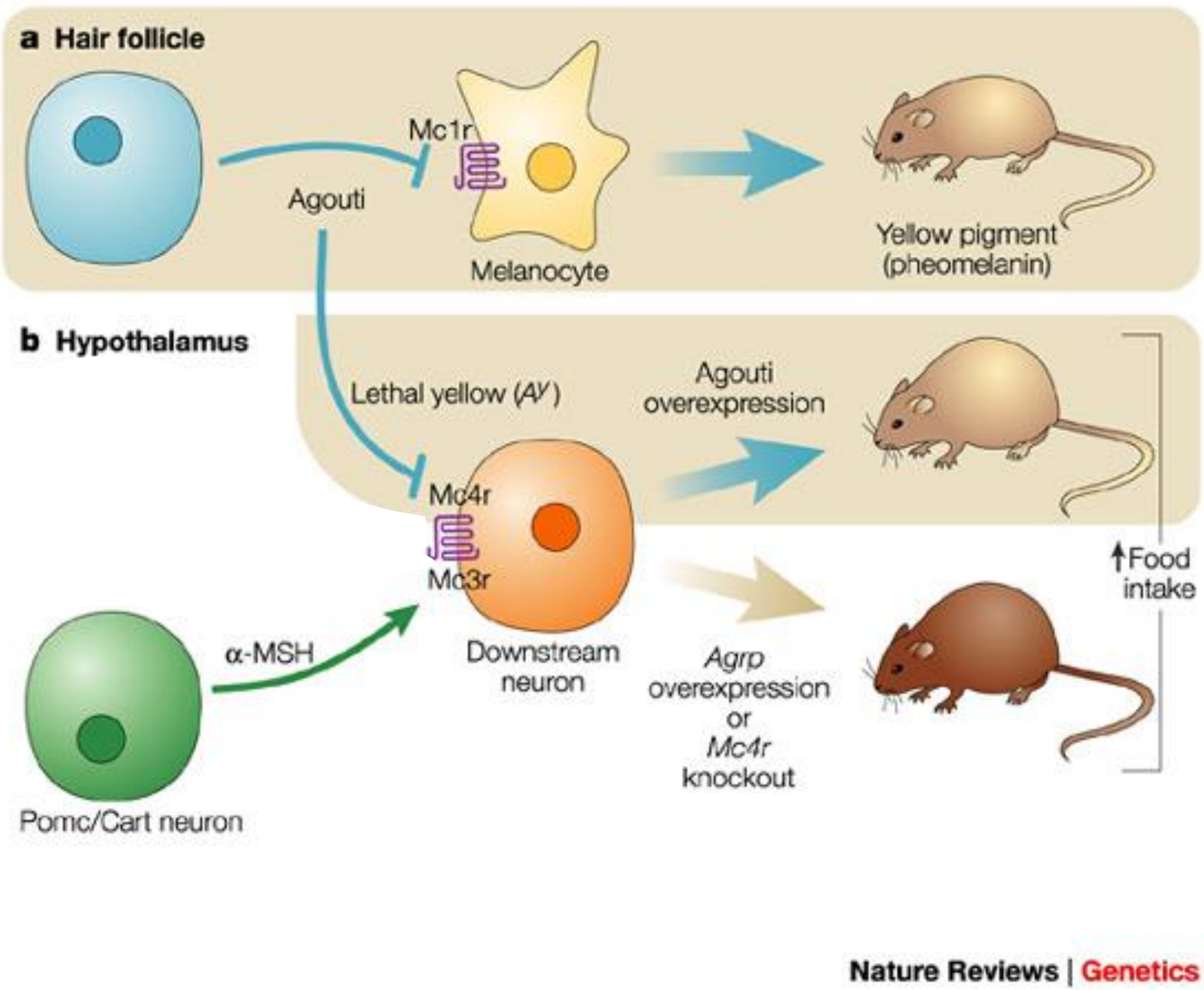
α-MSH = satiety signal

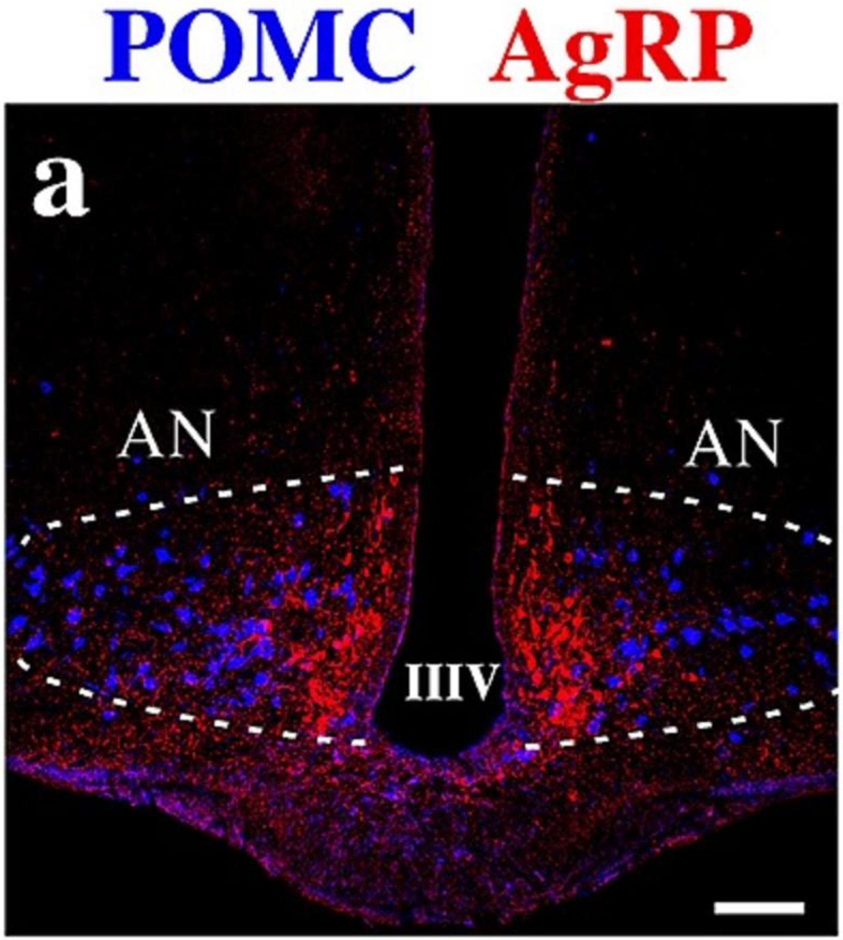


Agouti



Agouti related protein (AgRP)


a Hair follicle
Mc1r
Agouti
Melanocyte
Yellow pigment (pheomelanin)
b Hypothalamus
Lethal yellow (A^y)
Agouti overexpression
Mc4r
Mc3r
Downstream neuron
α-MSH
Pomc/Cart neuron
Agrp overexpression or Mc4r knockout
↑Food intake
Nature Reviews | Genetics



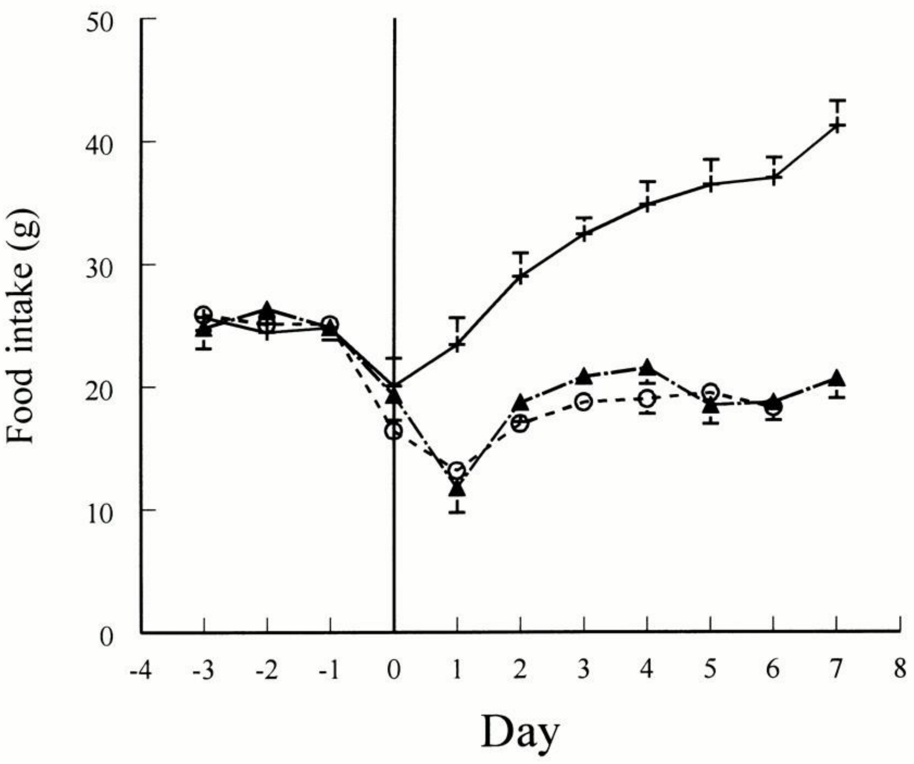
Both AgRP and POMC are localized in the arcuate nucleus (AN) of the hypothalamus.

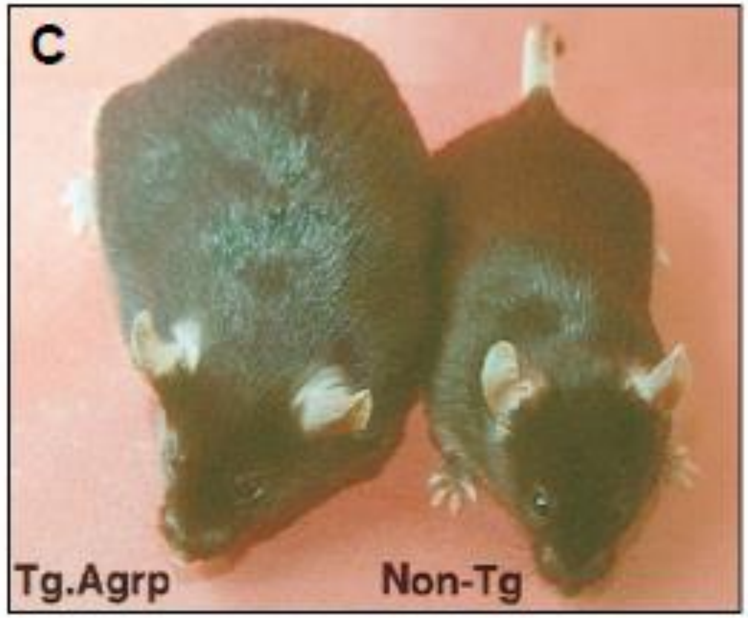
Daily food intake after chronic administration of 1 nmol/day AgRP (83-132) for 7 days.

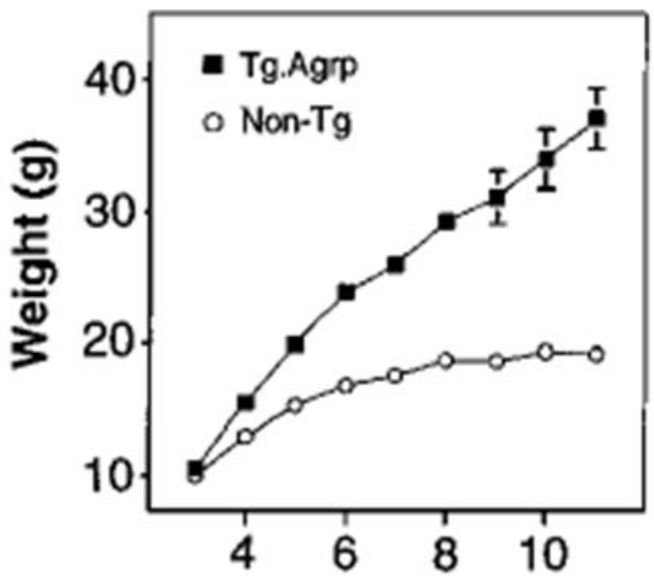
+, AgRP ad libitum fed group

▲, saline control group.

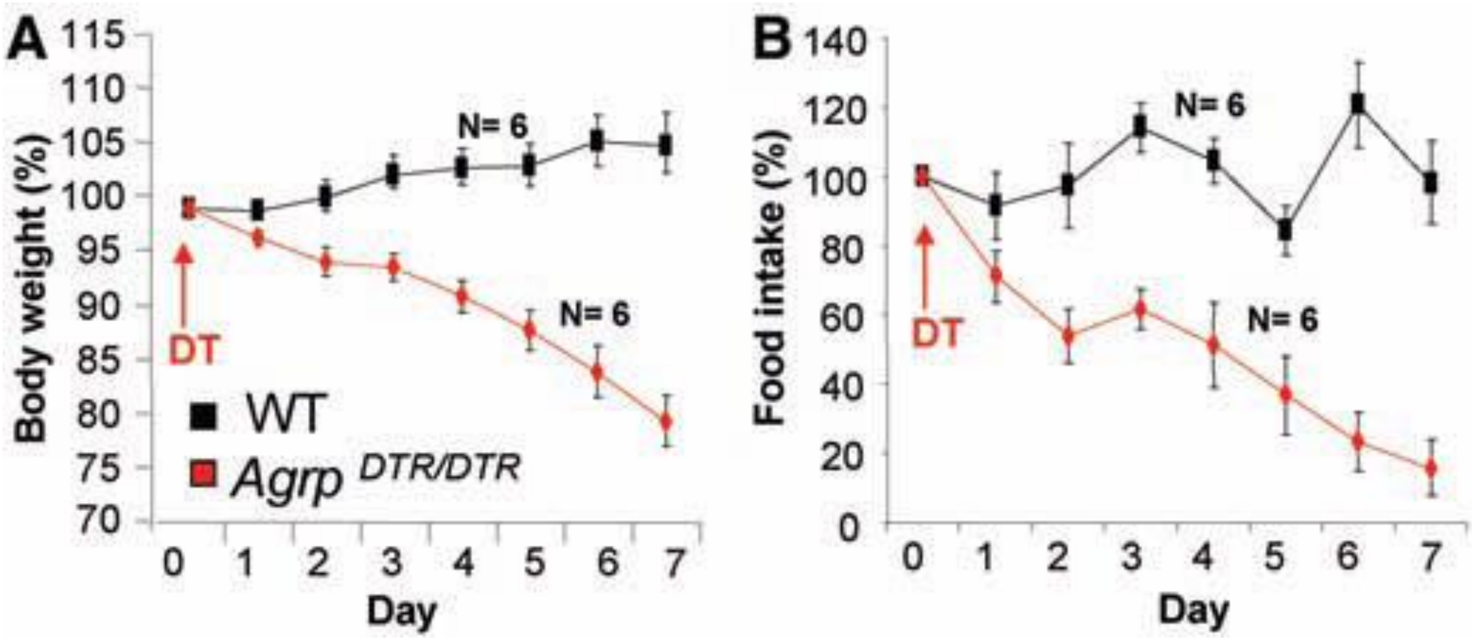
○, AgRP pair-fed group





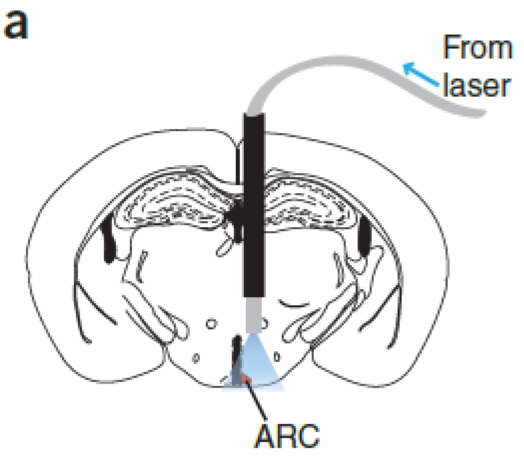


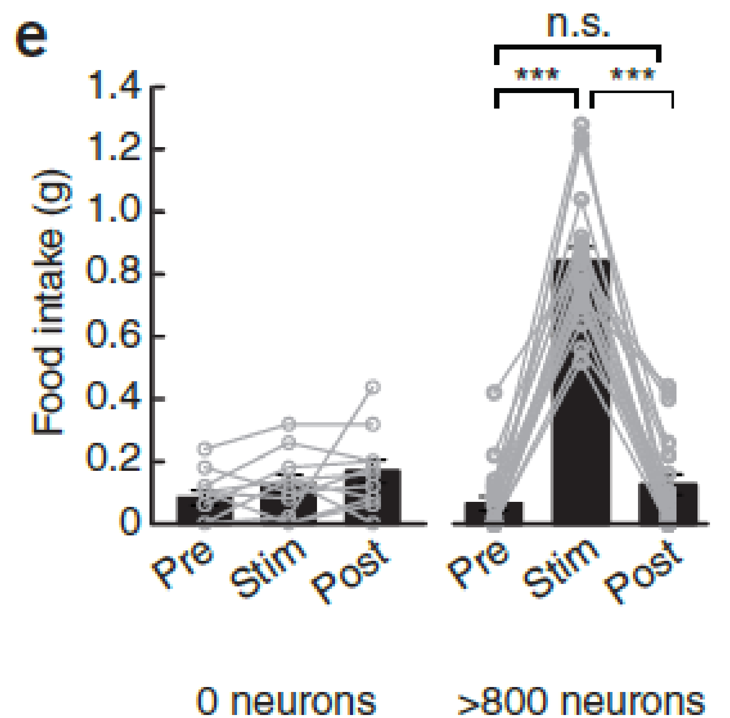
Ollmann et al., 1997



Luque et al. 2005

Activation of AgRP neurons leads to binge eating





Aponte et al., 2011

Transcripts that are highly expressed in the pineal gland

- Photoreception
- Circadian clock
- Melatonin synthesis

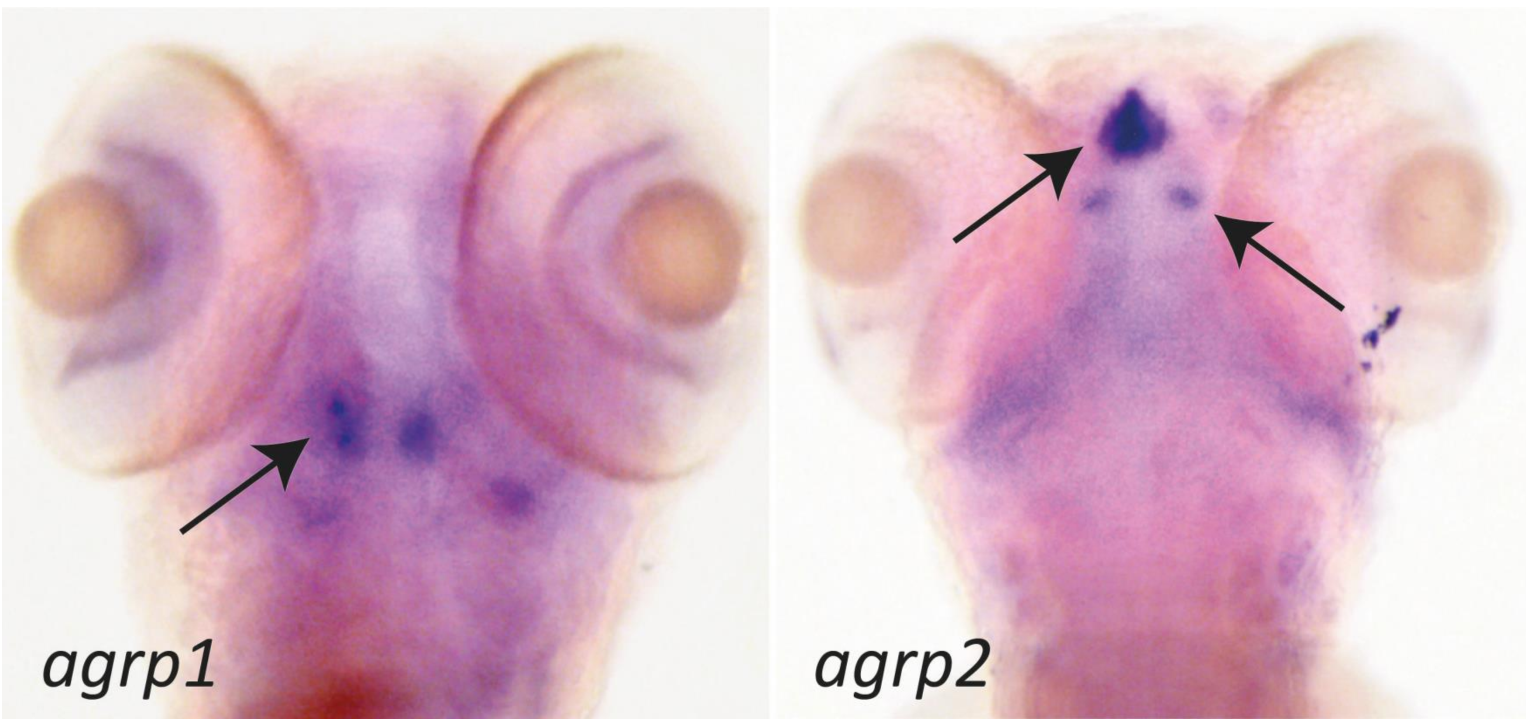
Table 1. A list of transcripts with high pineal expression, the 40 transcripts presented have the highest MFD.

Gene Symbol	MFD	ISH Image
*BG305792	260	
†Pdc2	215	** (Kobayashi *et al*., 2002)
*BI671344	200	
†Exorh	200	Pineal (Mano *et al*., 1999)
†Rbp4	185	
†Pde6a	170	** (Vihtelic *et al*., 2005)
†Gnat1	165	Pineal, Retina (Thisse *et al*., 2004)
†Pde6c	150	** (Vihtelic *et al*., 2005)
*BI671149	140	
*BI879853	120	
†Guk1	115	Pineal, Retina (Thisse *et al*., 2004)
†Zgc:92682	115	Pineal, Retina (Thisse *et al*., 2004)
†Opn1lw1	110	Pineal, Retina (Thisse *et al*., 2004)
Gucy2f	105	** (Brockerhoff *et al*., 2003)
†Aanat2	105	Pineal, Retina (Thisse *et al*., 2004)
†GngT1	90	Pineal, Retina (Thisse *et al*., 2004)
*AW826706	85	
†Zgc:73075	80	
†Tph1	80	Pineal (Thisse *et al*., 2004)
†Arr3	80	Pineal, Retina (Thisse *et al*., 2004)
†Zgc:73213	75	Pineal, Retina (Thisse *et al*., 2004)
*BG308558	75	
†Tph2	70	Pineal, Brain (Rauch *et al*., 2003)
*BI880166	70	
Elovl4	70	Pineal, Retina (Thisse *et al*., 2004)
†Slc25a31	70	Pineal, Retina, Background (Thisse *et al*., 2004)
Rlbp1l	70	Pineal, Retina (Thisse *et al*., 2004)
LOC563645	70	
†Arl3l2	65	Pineal, Retina (Thisse *et al*., 2004)
*BI671344	60	
†Crx	60	Pineal, Retina (Thisse *et al*., 2004)
*BI670871	55	
†Zgc:73310	50	** (Vihtelic *et al*., 2005)
*BI671248	45	
†Rcv1	45	Pineal, Retina (Thisse *et al*., 2004)
Ddc	45	Diencephalons, Midbrain (Thisse *et al*., 2004)
*BI881745	40	
zgc:73359	40	Pineal, Retina (Thisse *et al*., 2004)
nme2l	35	Pineal, Retina (Thisse *et al*., 2004)
*BG738656	35	

Alon et al. 2009

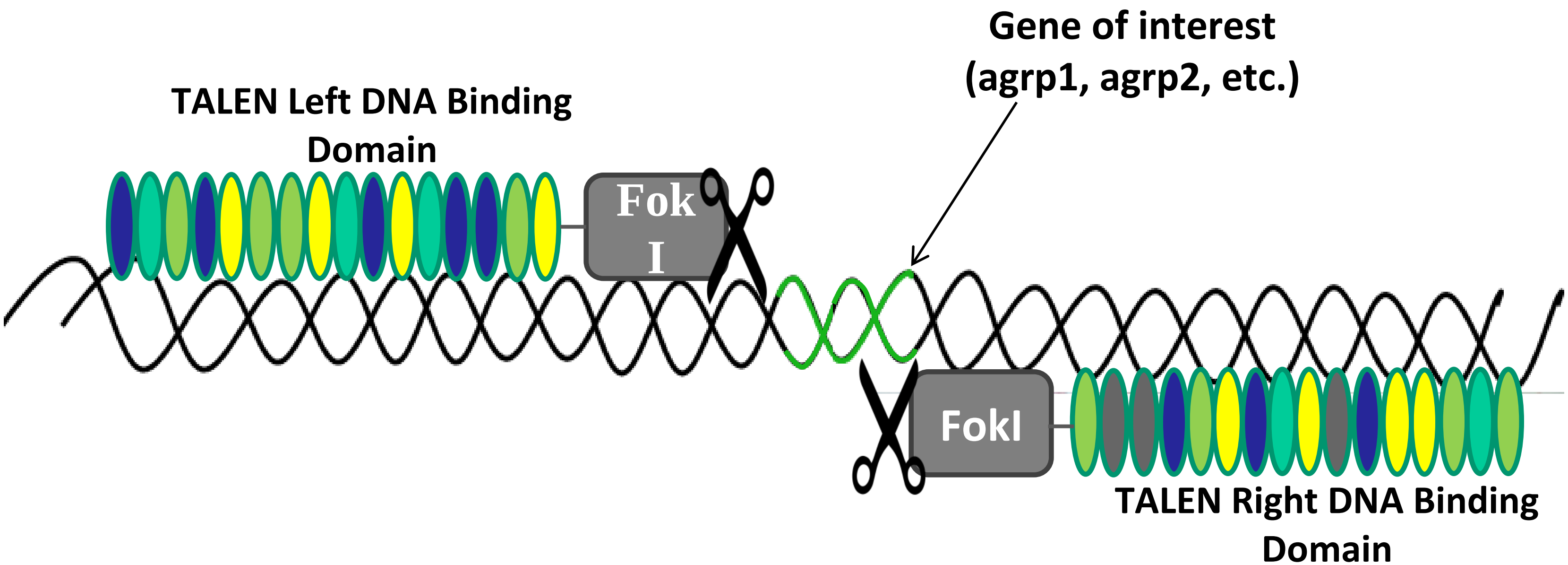
The unknown gene is a homologue of AgRP

Hypothalamic AgRP1 | Pineal AgRP2



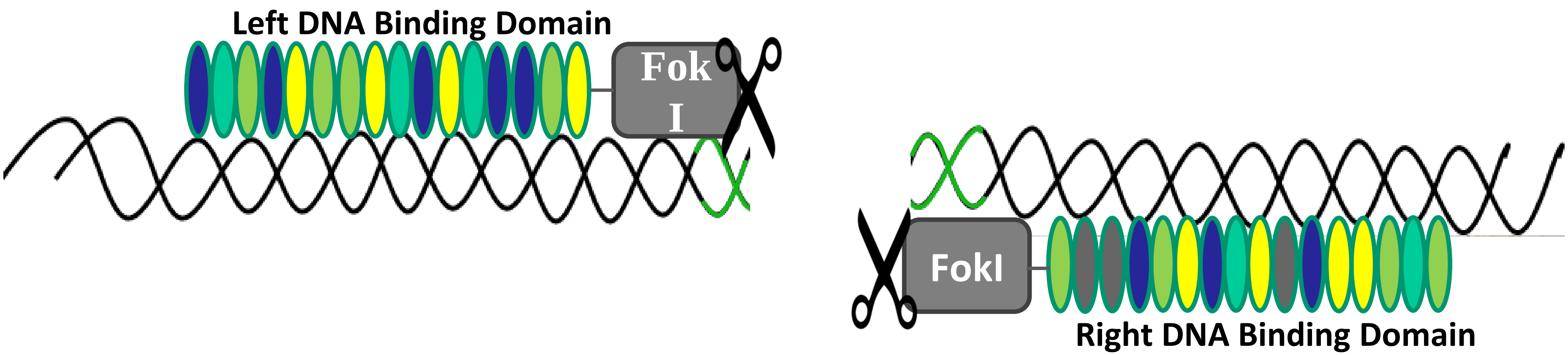
Shainer et al. 2017

TALEN-mediated Gene Knockout



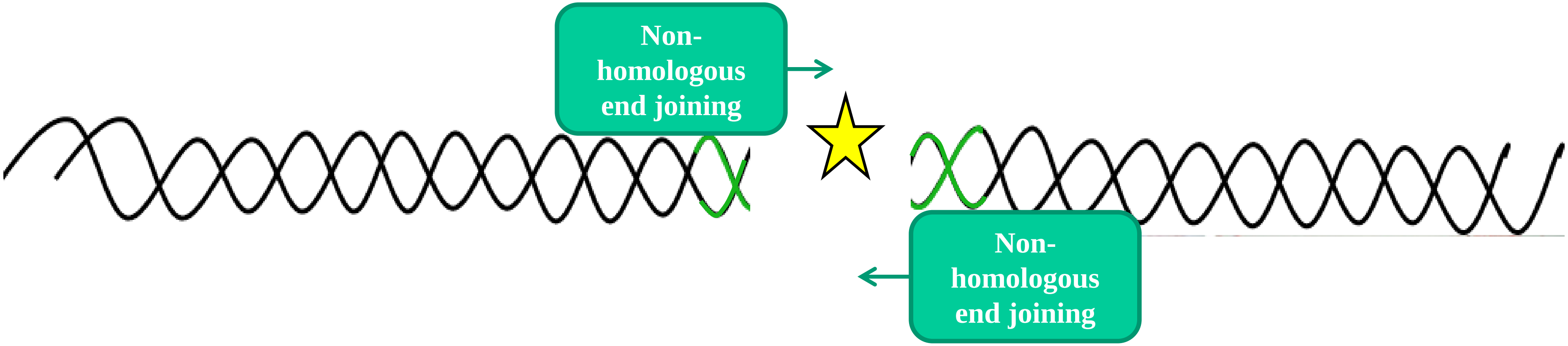
TALEN domains bind to a gene of interest and FOKI nucleases induce a double-stranded break.

TALEN-mediated Gene Knockout



TALEN domains bind to a gene of interest and FOKI nucleases induce a double-stranded break.

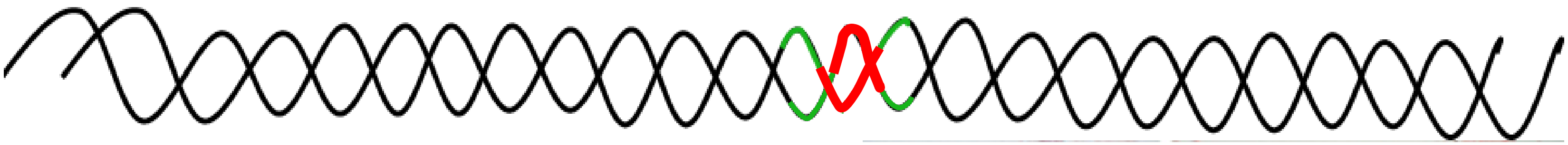
TALEN-mediated Gene Knockout



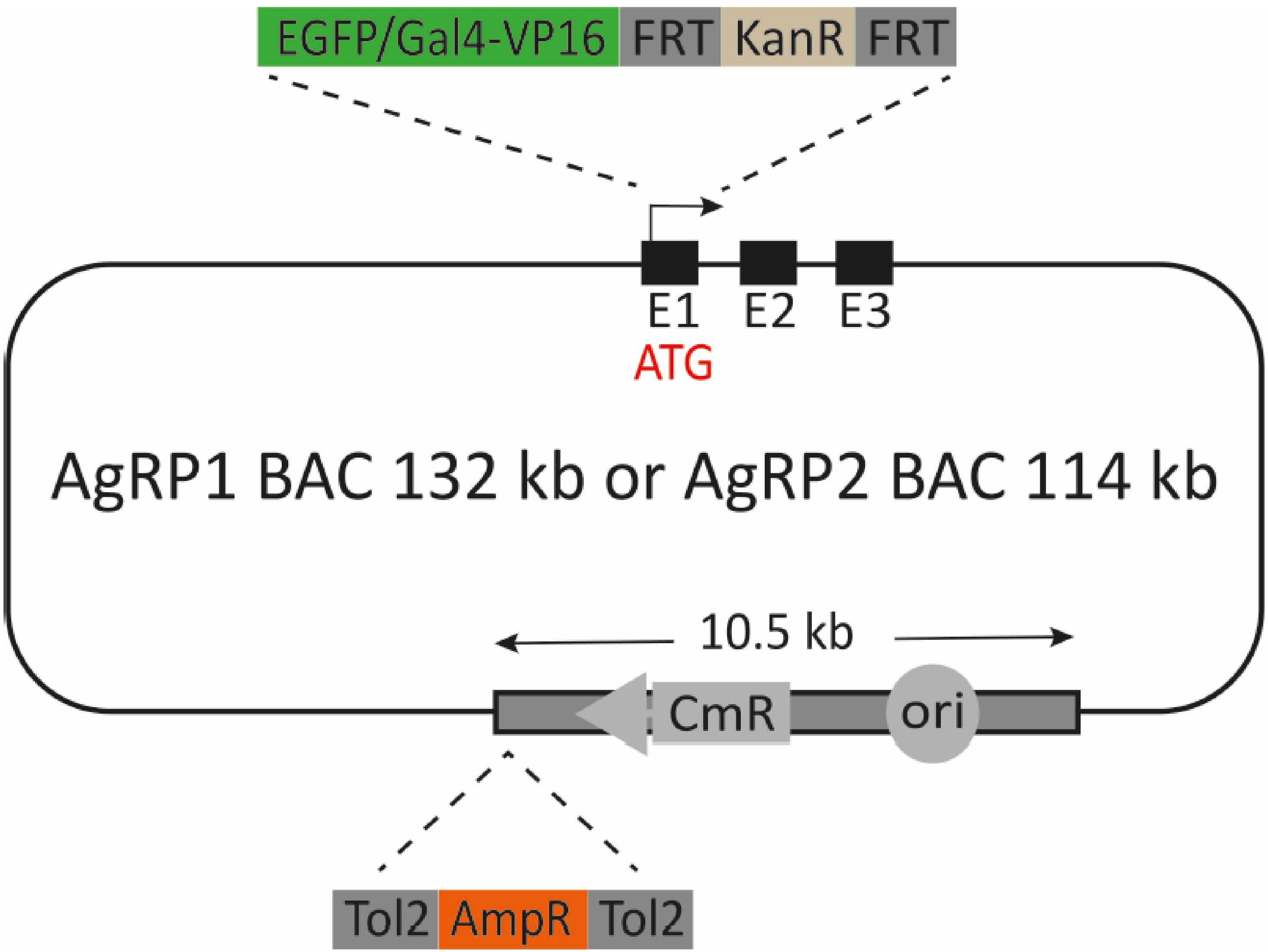
Non-homologous end joining (NHEJ) repair system introduces indels (insertions and/or deletion) into the gene sequence.

TALEN-mediated Gene Knockout

Mutated (inherited) gene sequence (agrp1, agrp2, etc.)

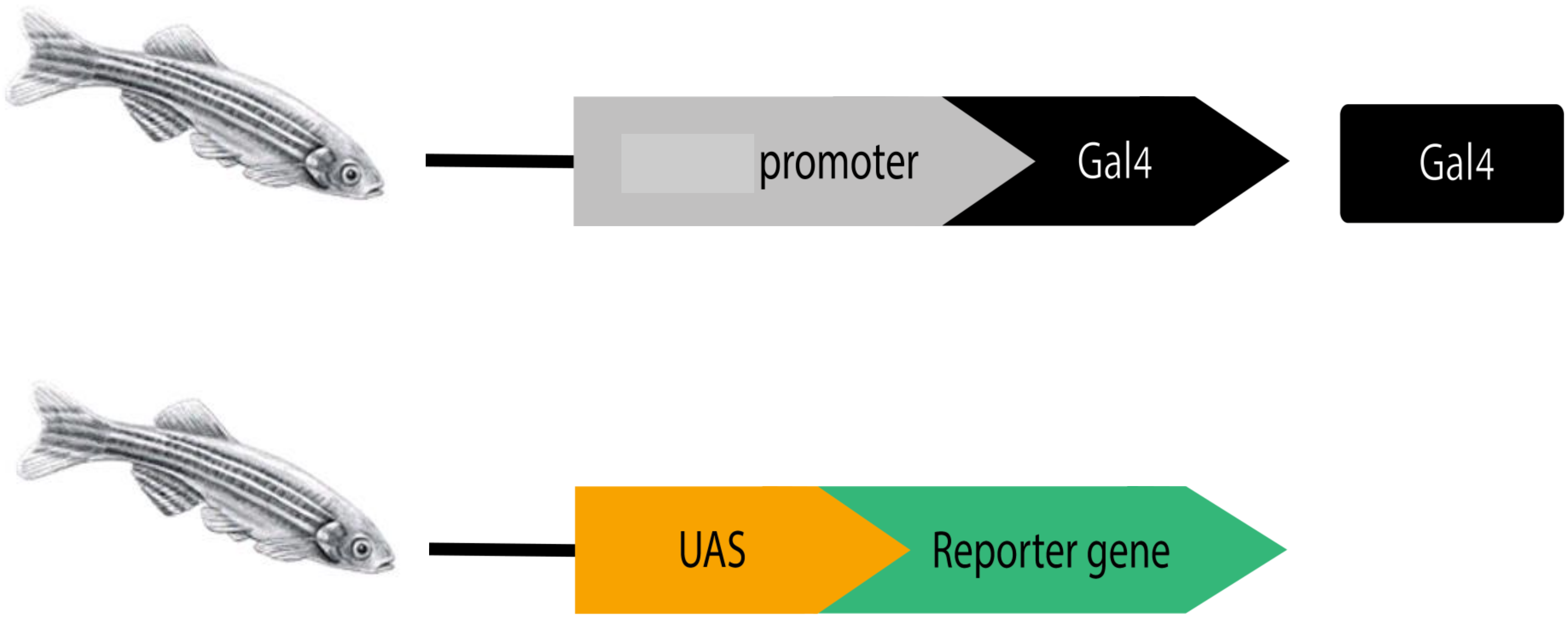


Non-homologous end joining (NHEJ) repair system introduces indels (insertions and/or deletion) into the gene sequence.

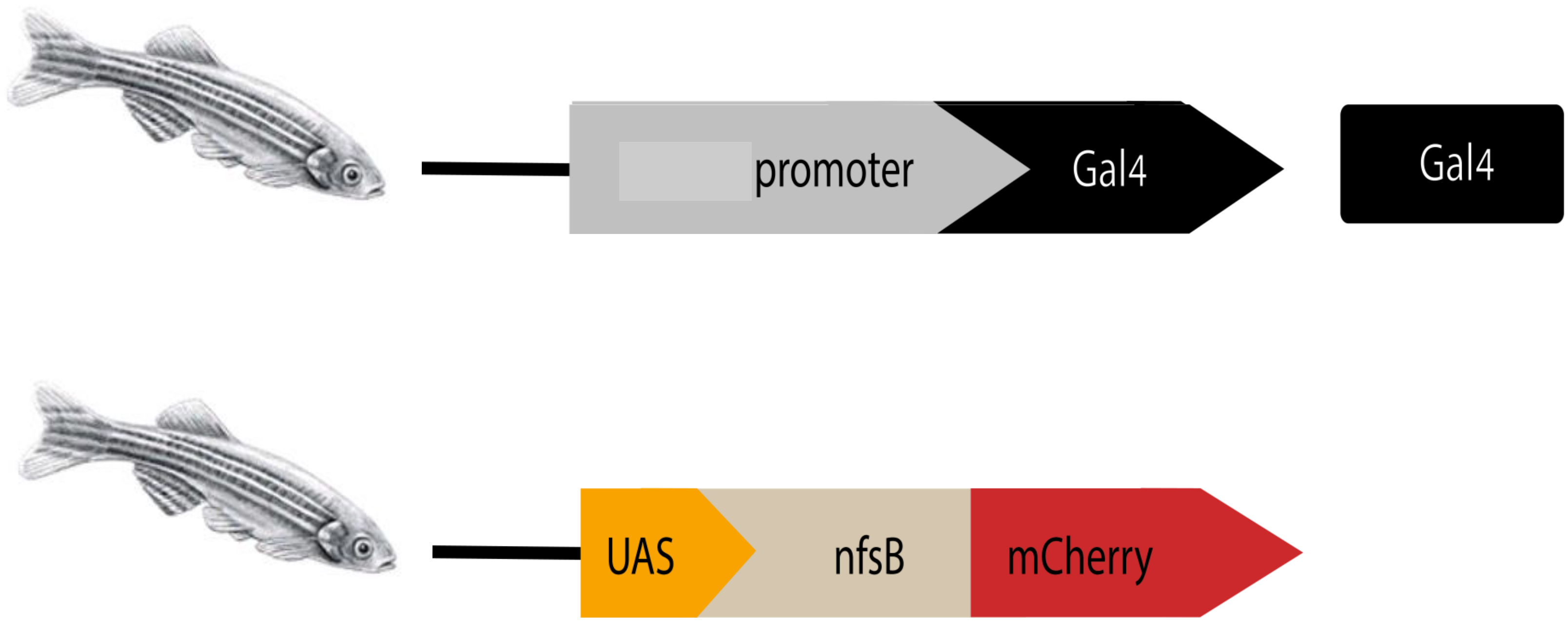


Shainer et al. 2017

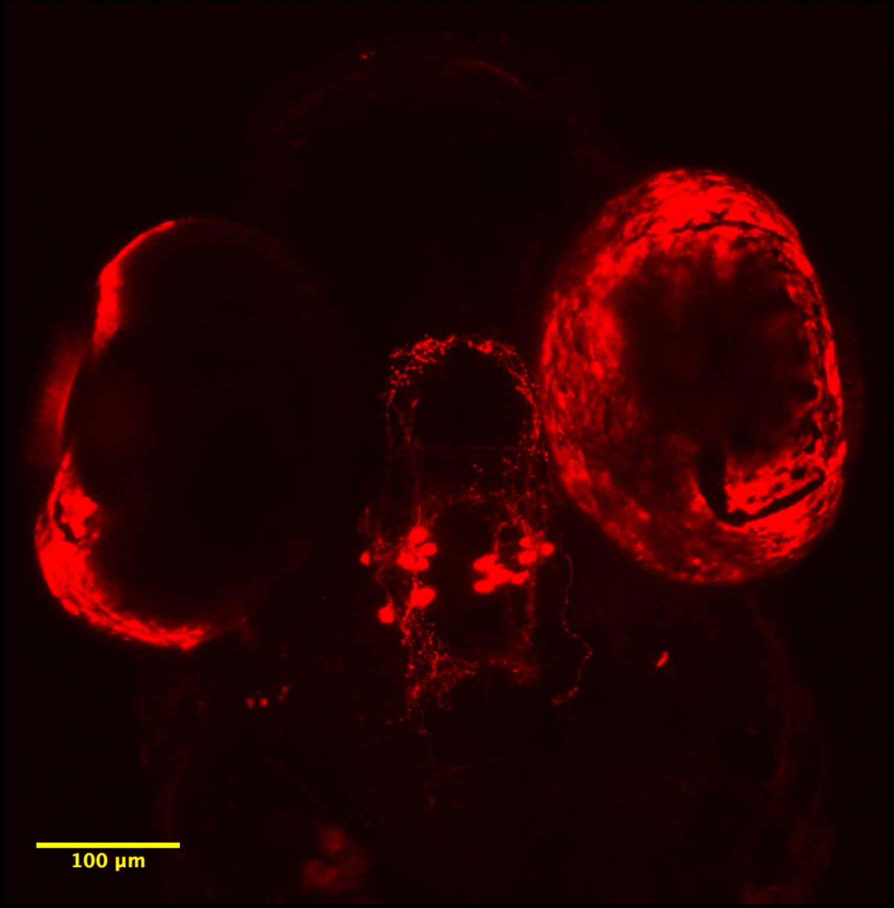
The GAL4-UAS system



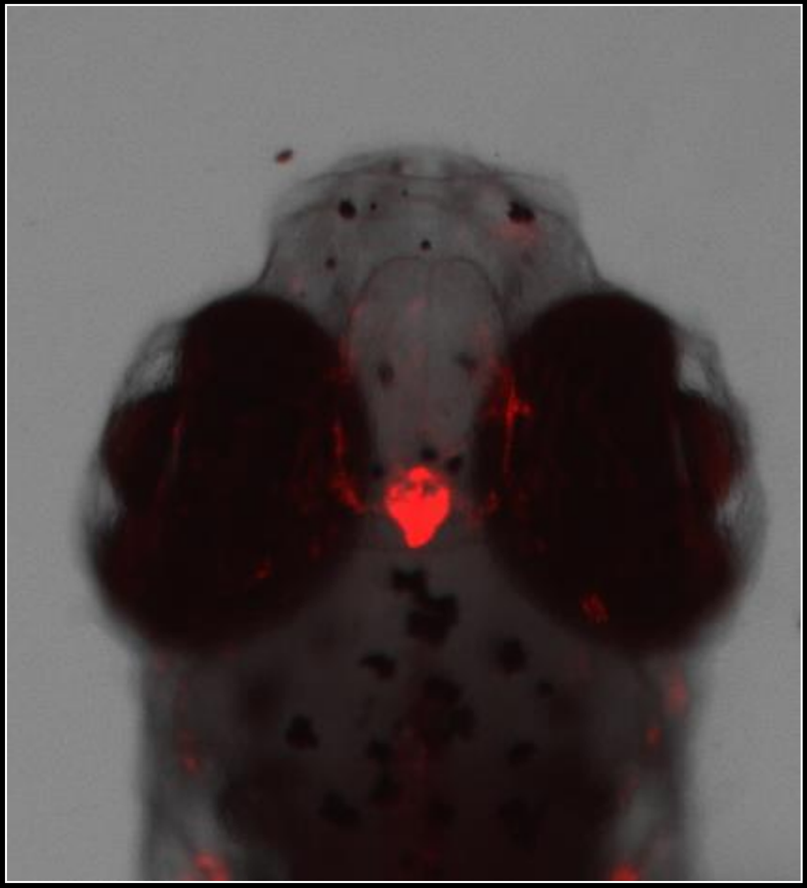
The GAL4-UAS system



agrp1 transgenic fish

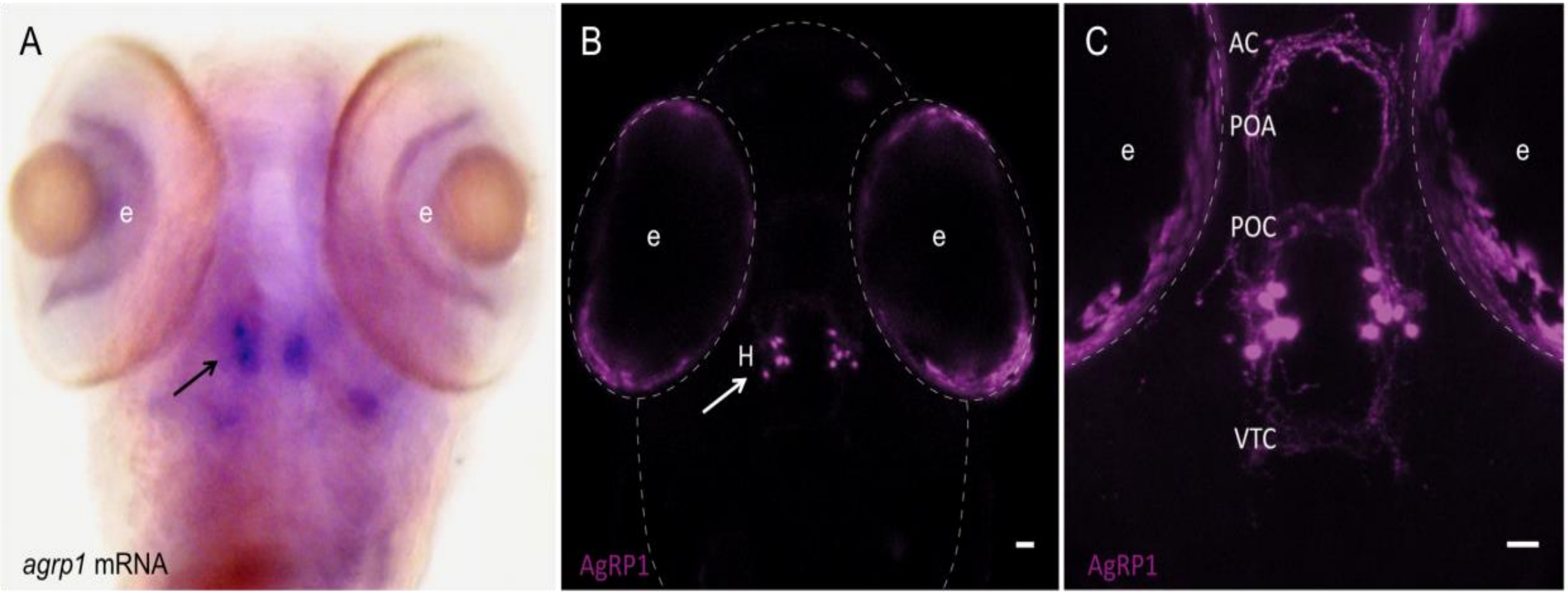


agrp2 transgenic fish



Shainer et al. 2017

The *agrp1* transgenic line



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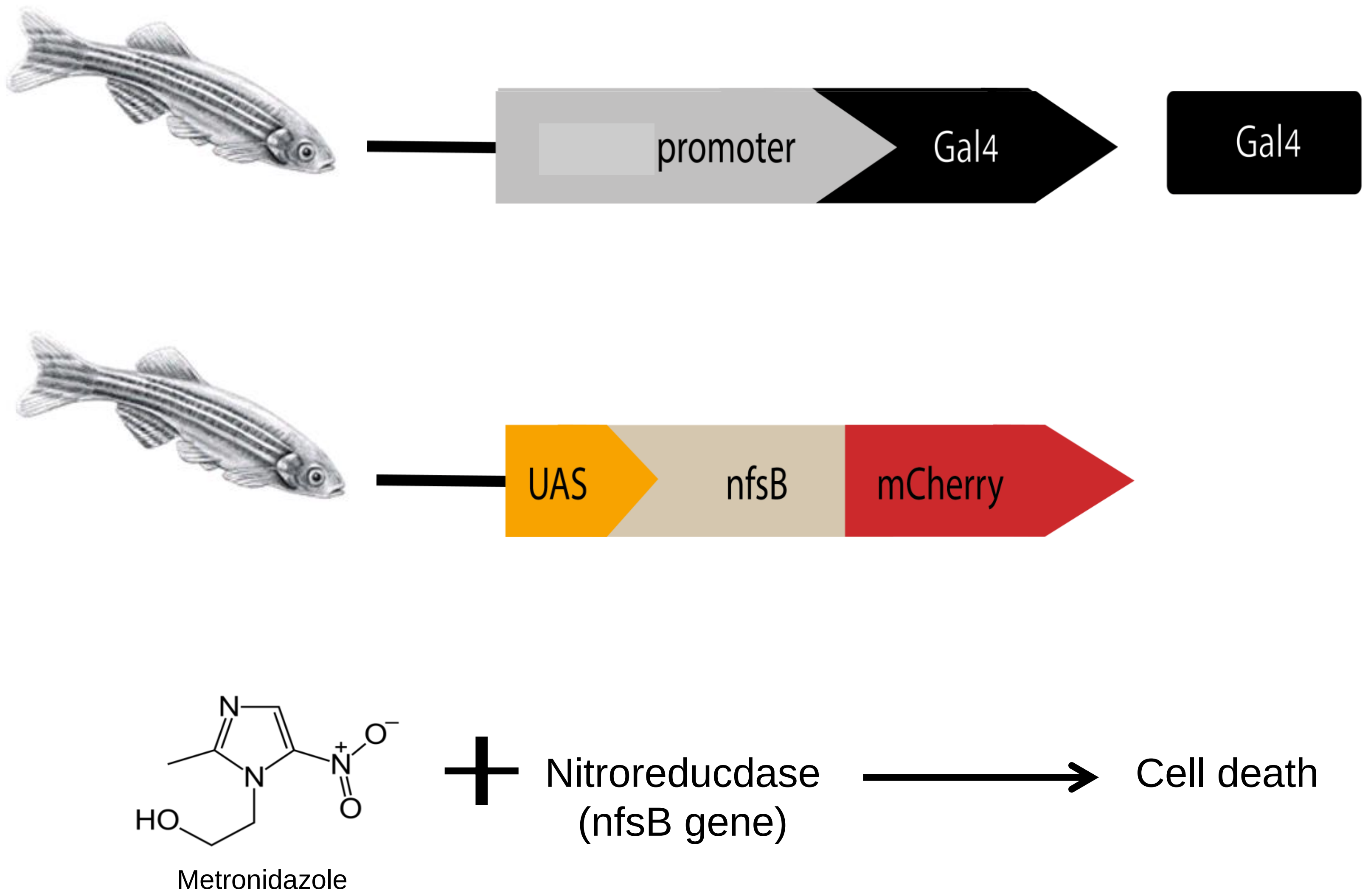
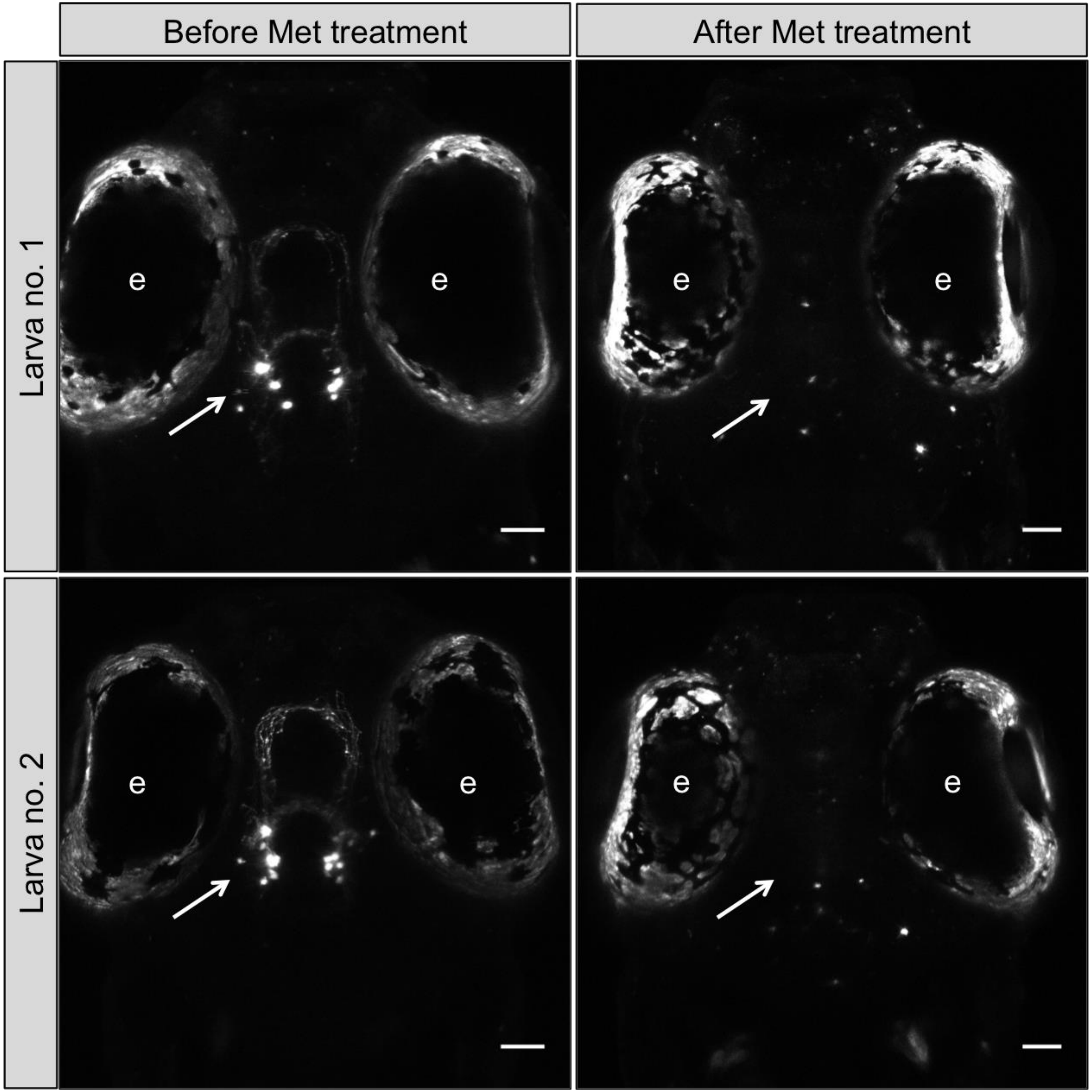
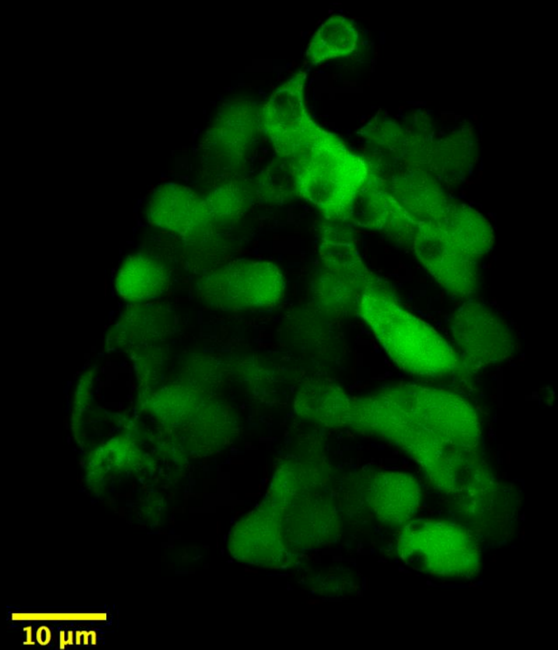
Neuronal ablation



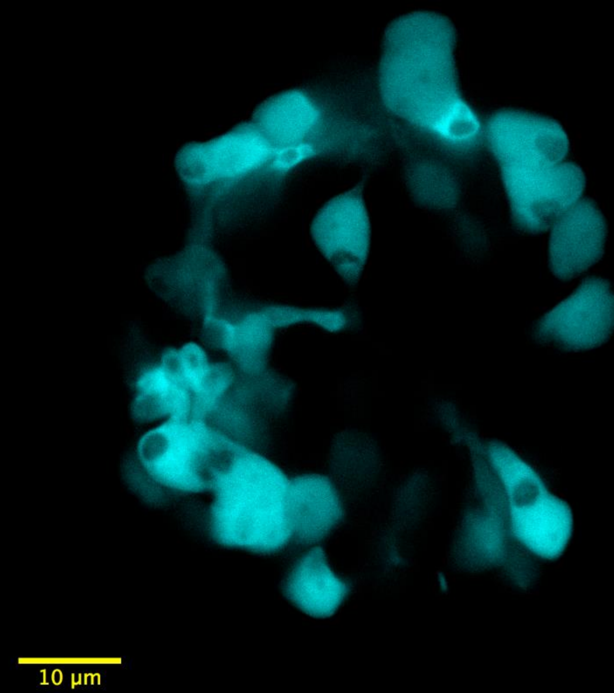


Before Met treatment
After Met treatment
Larva no. 1
Larva no. 2
e
e
e
e
e
e
e
e

Pineal photoreceptor cells vs. projection neurons



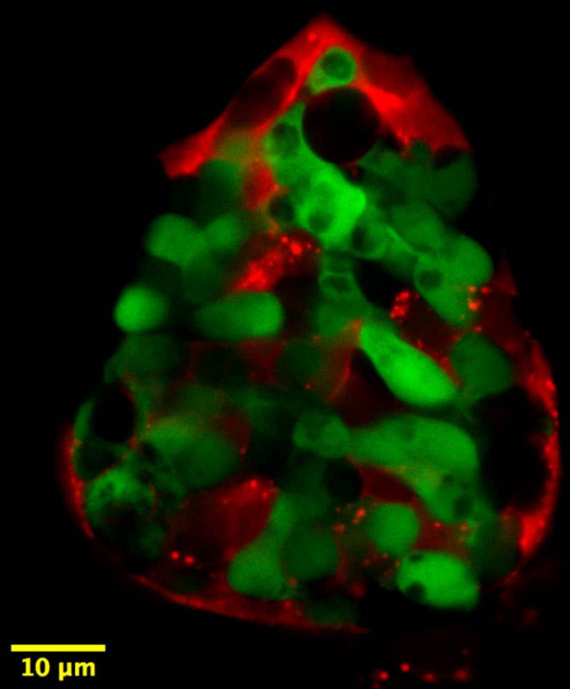
Photoreceptors
(*aanat2*)



Projection neurons
(*foxd3*)

Shainer et al. 2017

A third subset of pineal cells: AgRP2 cells



Photoreceptors
(*aanat2*)

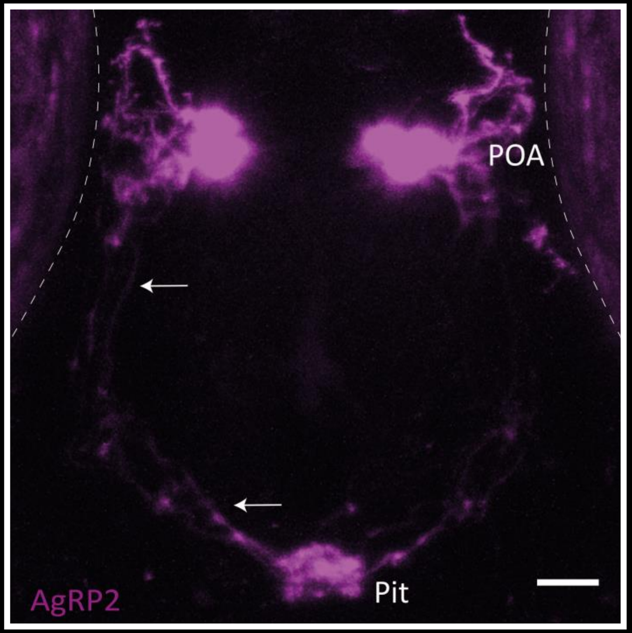
AgRP2

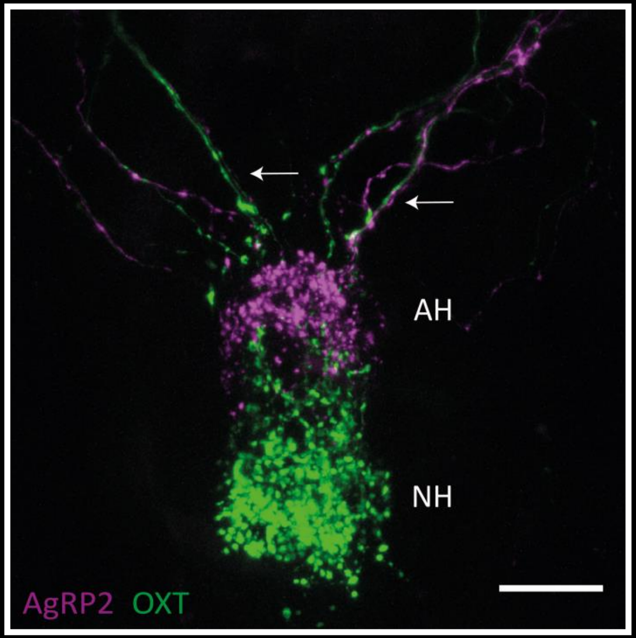
Projection neurons
(*foxd3*)

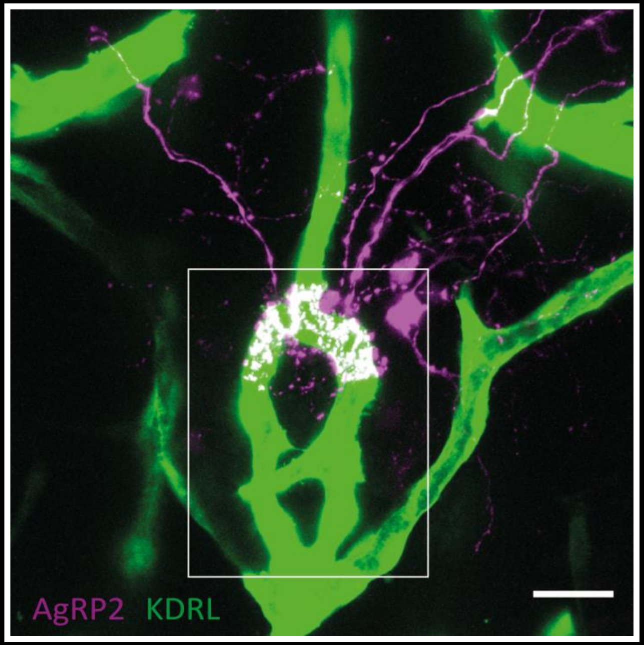
AgRP2

Shainer et al. 2017

Shainer et al. 2017







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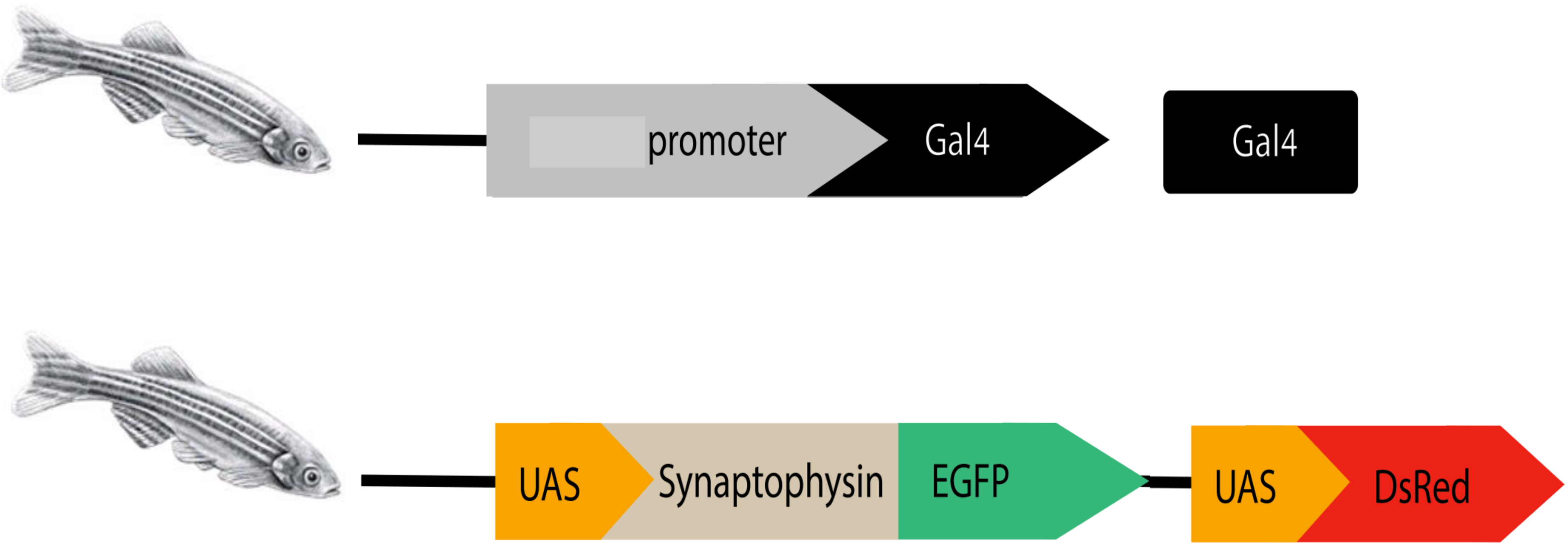
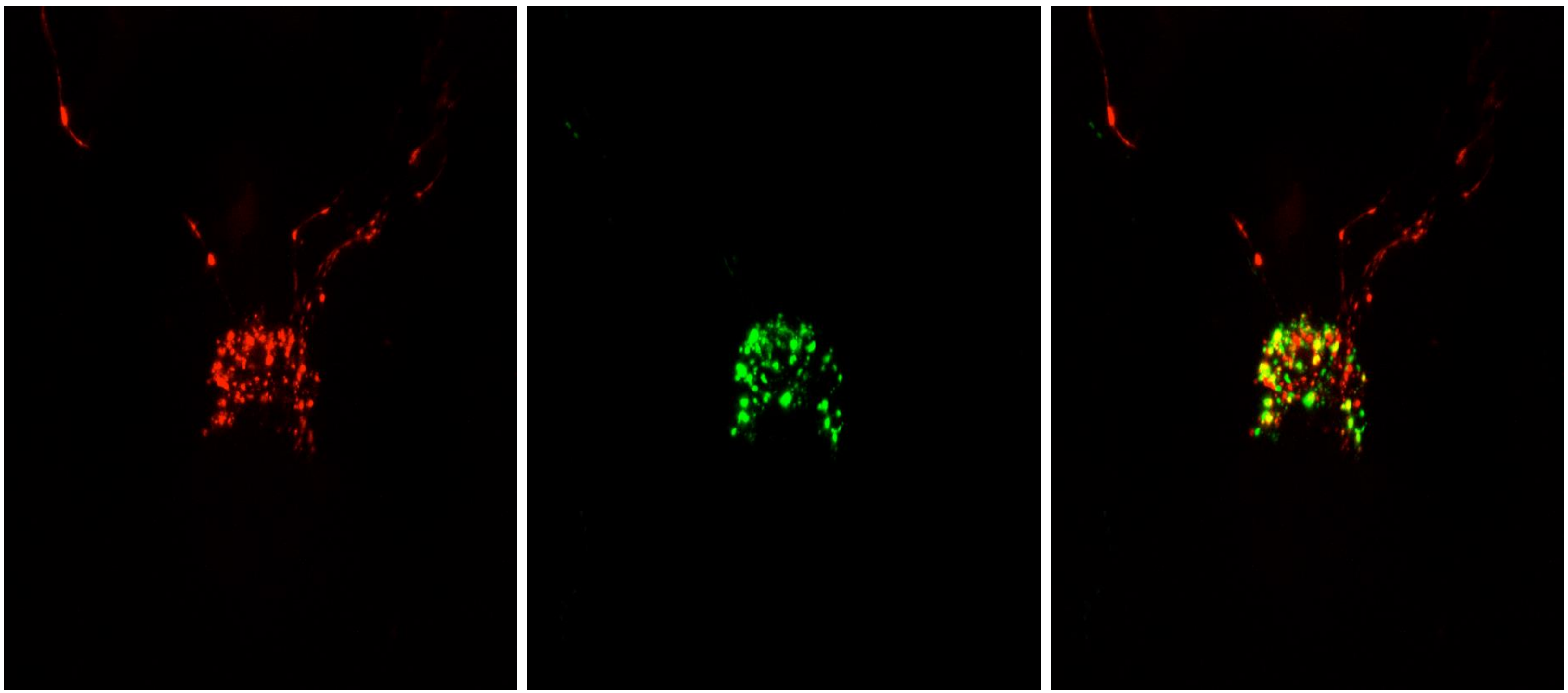
Synaptic plasticity





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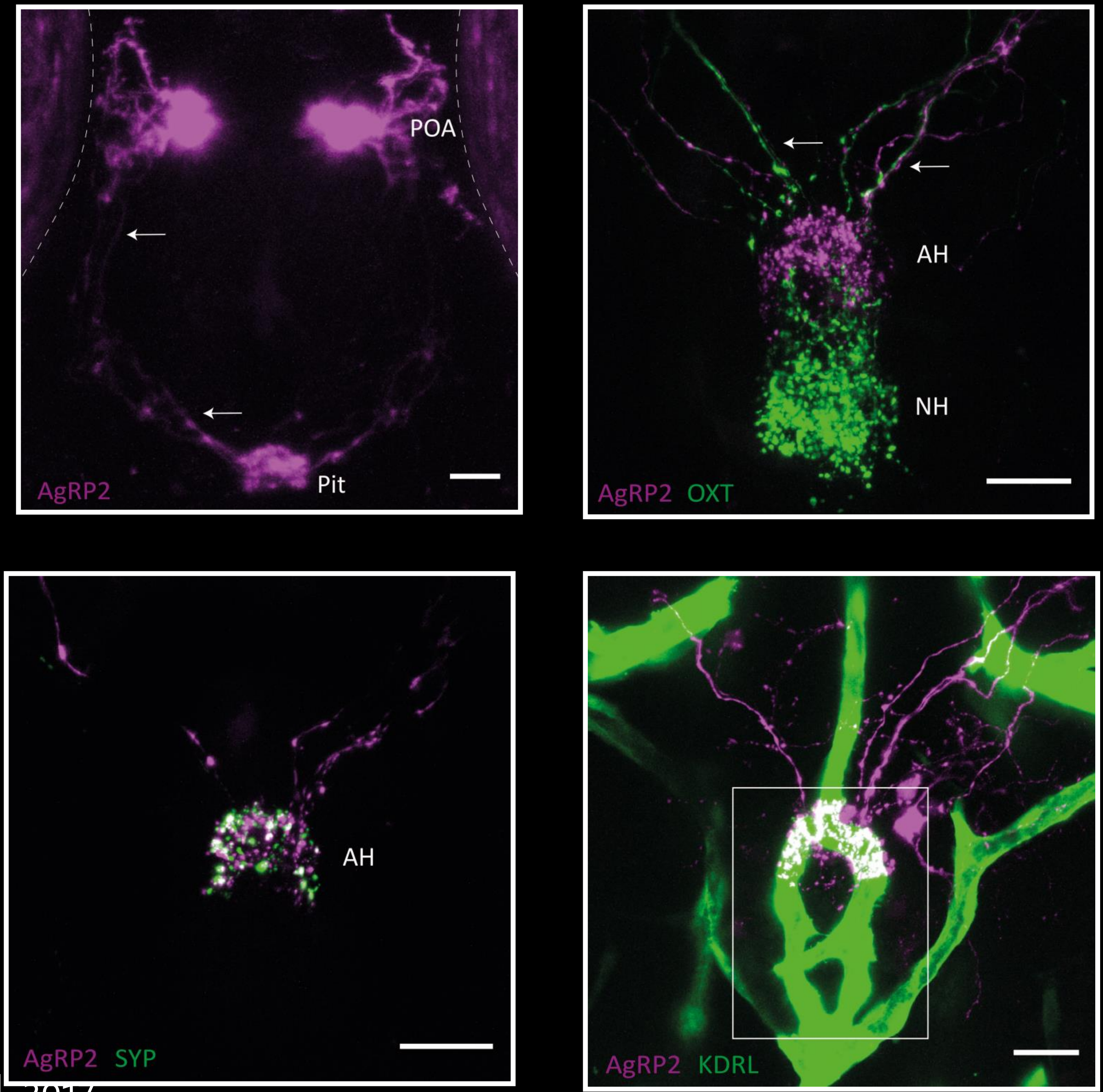

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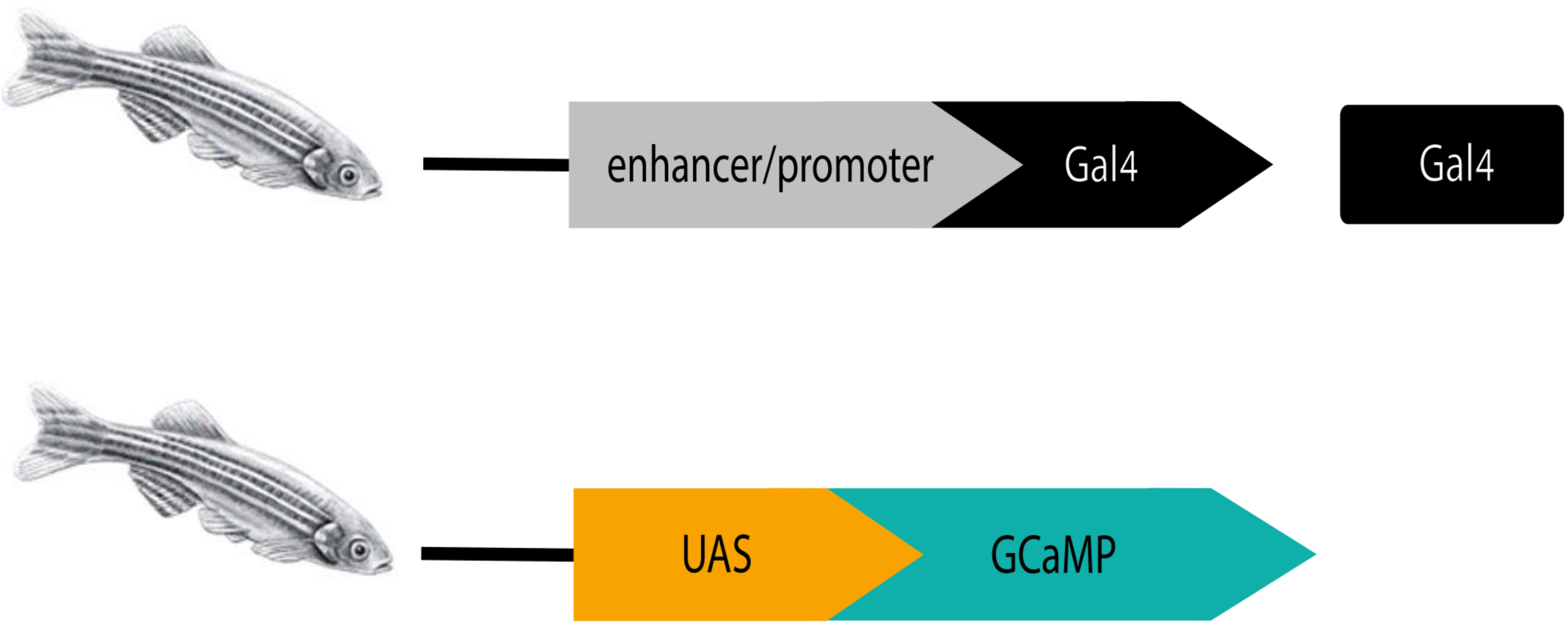
Seeing neurons in action, using Ca^{++} sensor



https://www.youtube.com/watch?v=1Q-g1uCvYOA

Optogenetically activating neurons