file:“Lecture_Hunger_Week8_2025.pdf“

Course „Neural Circuits of motivated behavior“

Internal body states and associated behaviors: hunger and feeding (Week 8)

Olexiy Kochubey

Thursday 10.04.2025

Outlook

I. Energy homeostasis and metabolism

a) biological energy sources

b) glucose, its role and regulation

II. Neural circuits of hunger and satiety

a) bodily signals of energy state

b) sensing of satiety / hunger signals by POMC and AgRP neurons

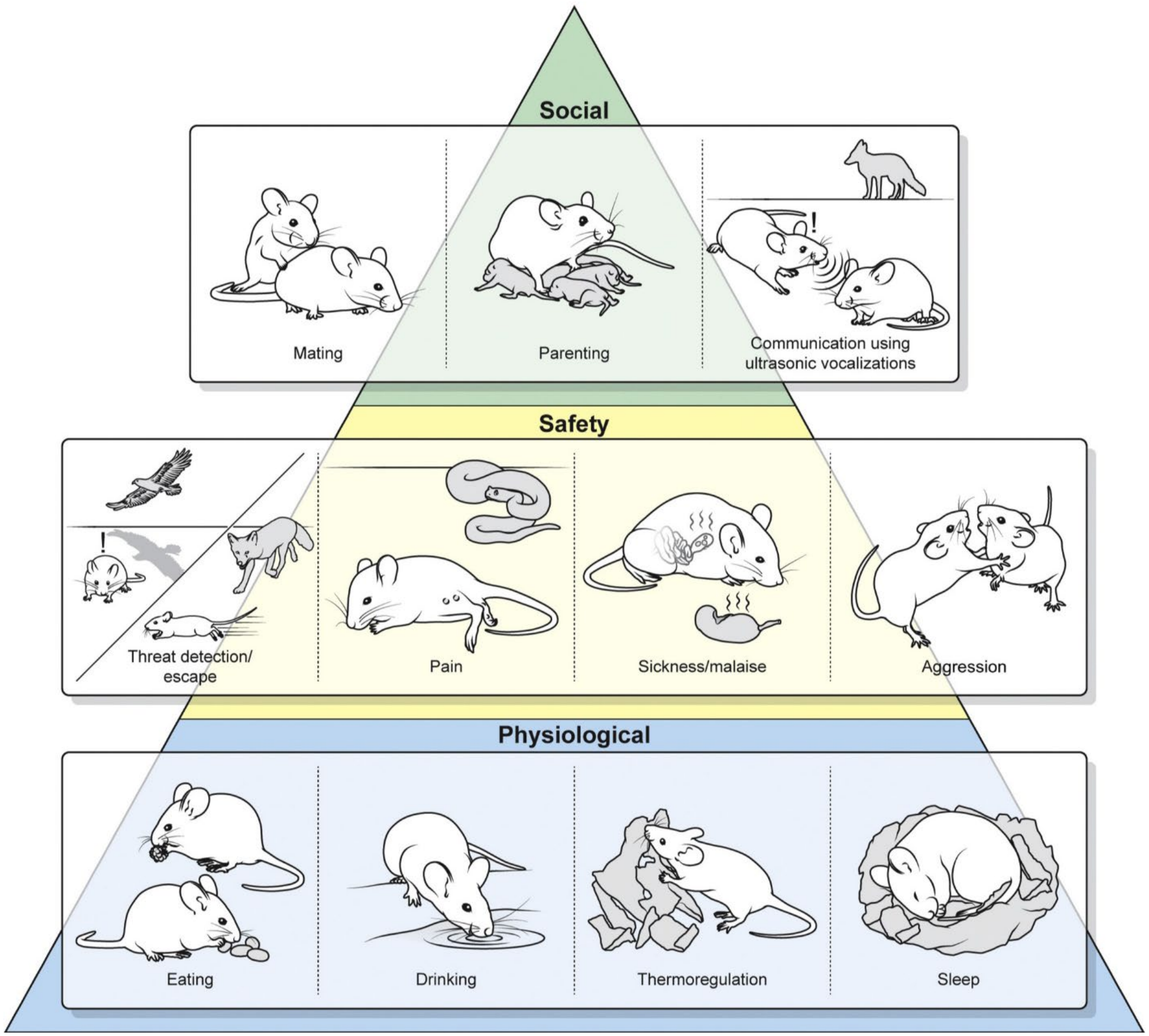
c) balancing function of the ARC (the arcuate nucleus) in feeding control

d) local- and long-range inhibition by the AgRP arcuate neurons in feeding behavior

e) role of PVH in regulation of appetite

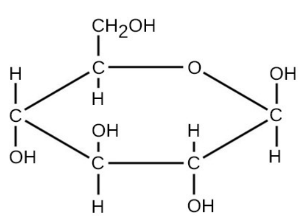
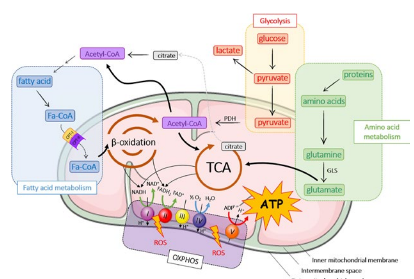
f) motivational valency of hunger and satiety imposed by the ARC-PVH circuit

Eating (= energy intake) is one of the most basic needs of any organism

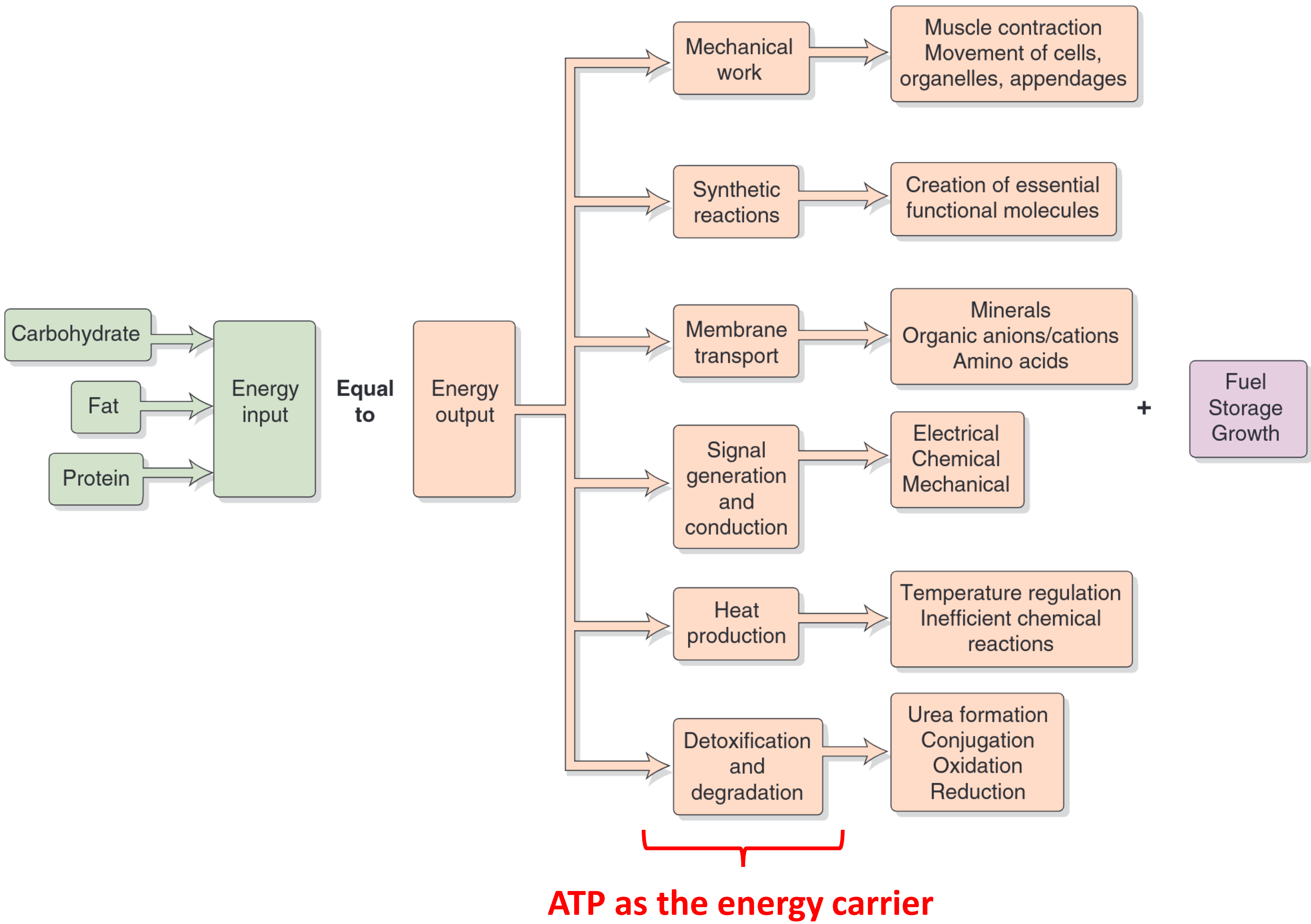


after Sutton & Krashes 2020

Energy transformation by biological organisms

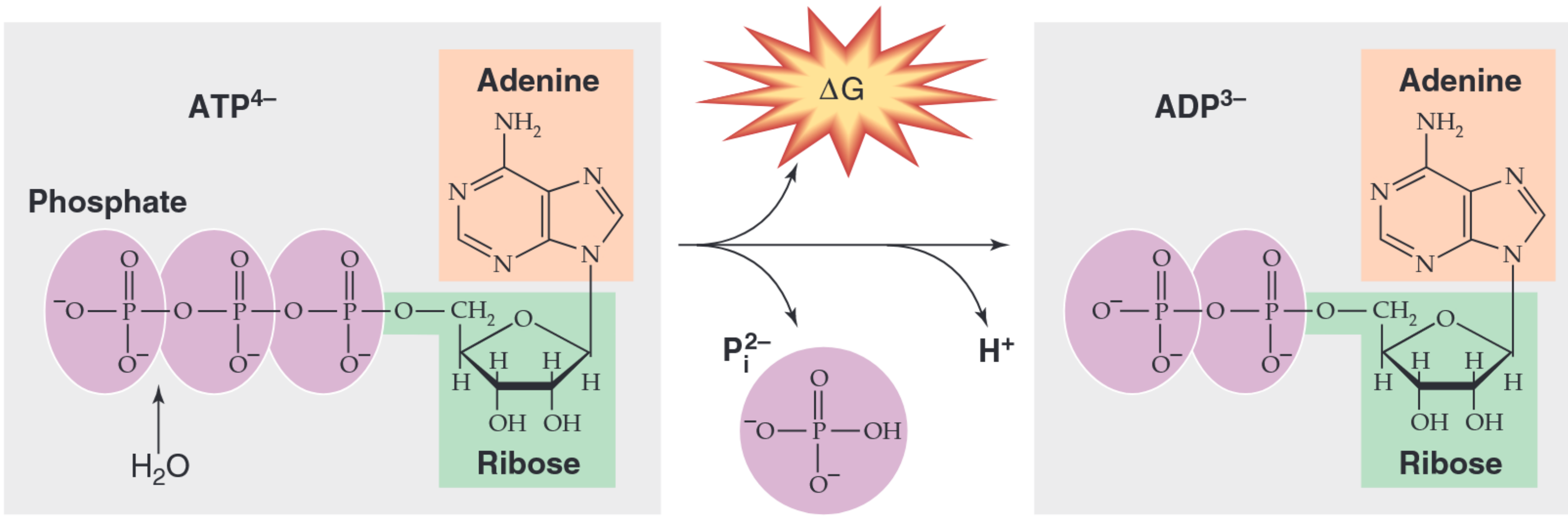
Energy source	Transformation (+ O_2)	Waste end-products
 chemical	 thermal + mechanical	 CO_2 + H_2O
 chemical	 thermal + mechanical	 CO_2 + H_2O
 chemical	 chemical + thermal + mechanical	 CO_2 + H_2O

Energy transformation, management and conservation by an organism



Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 58-4

ATP is the universal molecular energy carrier („energy currency“)



$$\underbrace{\Delta E}_{\text{Total energy (Enthalpy)}} = \underbrace{\Delta G}_{\text{Gibb´s free energy}} + \underbrace{T \cdot \Delta S}_{\text{Thermic waste}}$$

Total energy (Enthalpy) — **Gibb´s free energy** — **Thermic waste**

Gibb´s free energy: -28 to -34 kJ/mol ATP

Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 58-5

Glucose is an upstream biochemical substrate for generation of ATP

TABLE 58-4 Generation of ATP from the Complete Oxidation of Glucose*

Glycolysis $\xrightarrow{\textit{direct}}$	2 ATP
Glycolysis → 2 × 1 NADH $\xrightarrow{\textit{ox. phos.}}$	3 or 5 ATP
2 × (Pyruvate → acetyl CoA) → 2 NADH $\xrightarrow{\textit{ox. phos.}}$	5 ATP
Citric acid cycle → 2 × 1 GTP $\xrightarrow{\textit{direct}}$	2 ATP
Citric acid cycle → 2 × 3 = 6 NADH $\xrightarrow{\textit{ox. phos.}}$	15 ATP
Citric acid cycle → 2 × 1 = 2 $FADH_2$ $\xrightarrow{\textit{ox. phos.}}$	3 ATP
Total	30 or 32 ATP per glucose

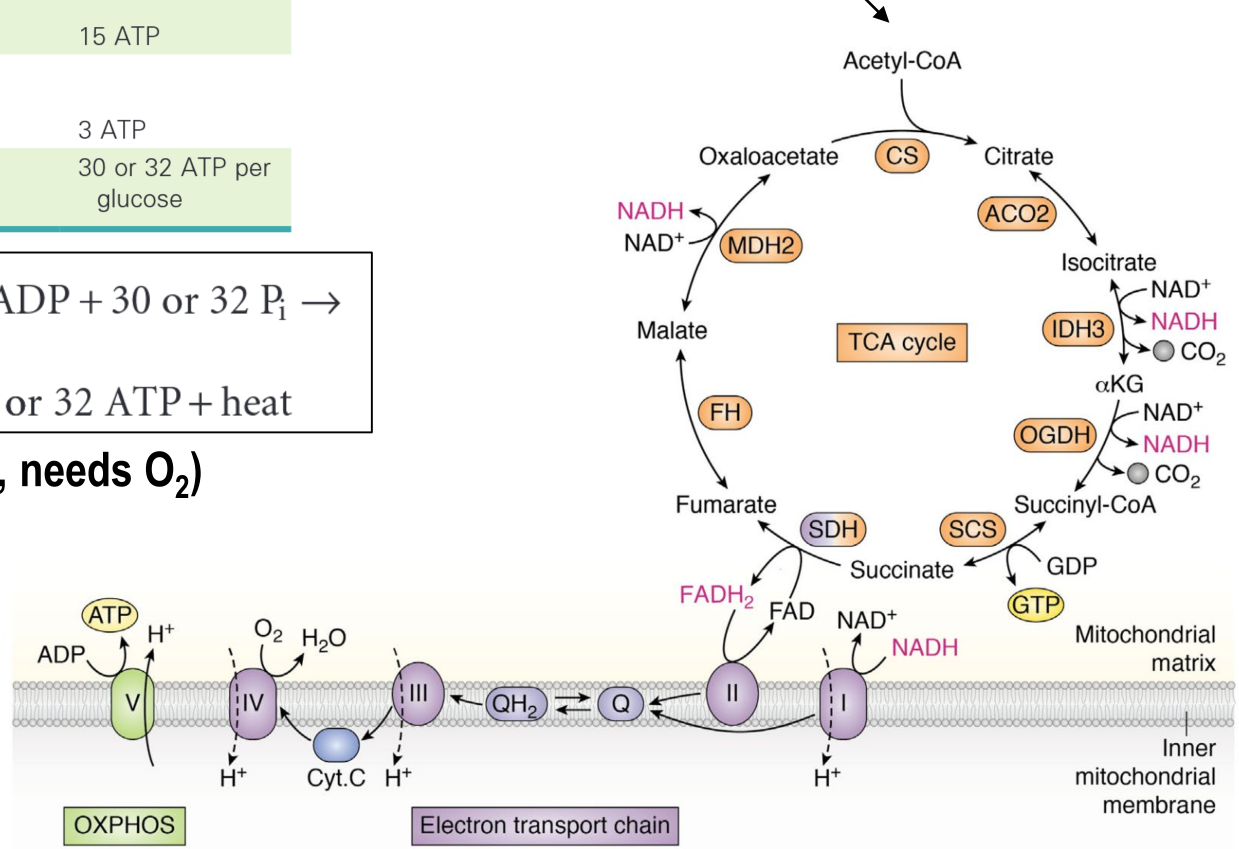
$$\underset{\textit{Glucose}}{C_6H_{12}O_6} + 6\,O_2 + 30 \text{ or } 32\ ADP + 30 \text{ or } 32\ P_i \rightarrow 6\,CO_2 + 6\,H_2O + 30 \text{ or } 32\ ATP + \text{heat}$$

(aerobic oxydation, needs O_2)

(anaerobic lysis, w/o O_2)

GLYCOLYSIS

$$1\ \text{Glucose} + 2\ ADP + 2\ P_i + 2\ NAD^+ \downarrow 2\ \text{Pyruvate} + 2\ ATP + 2\ NADH + 2\ H^+ + 2\ H_2O$$



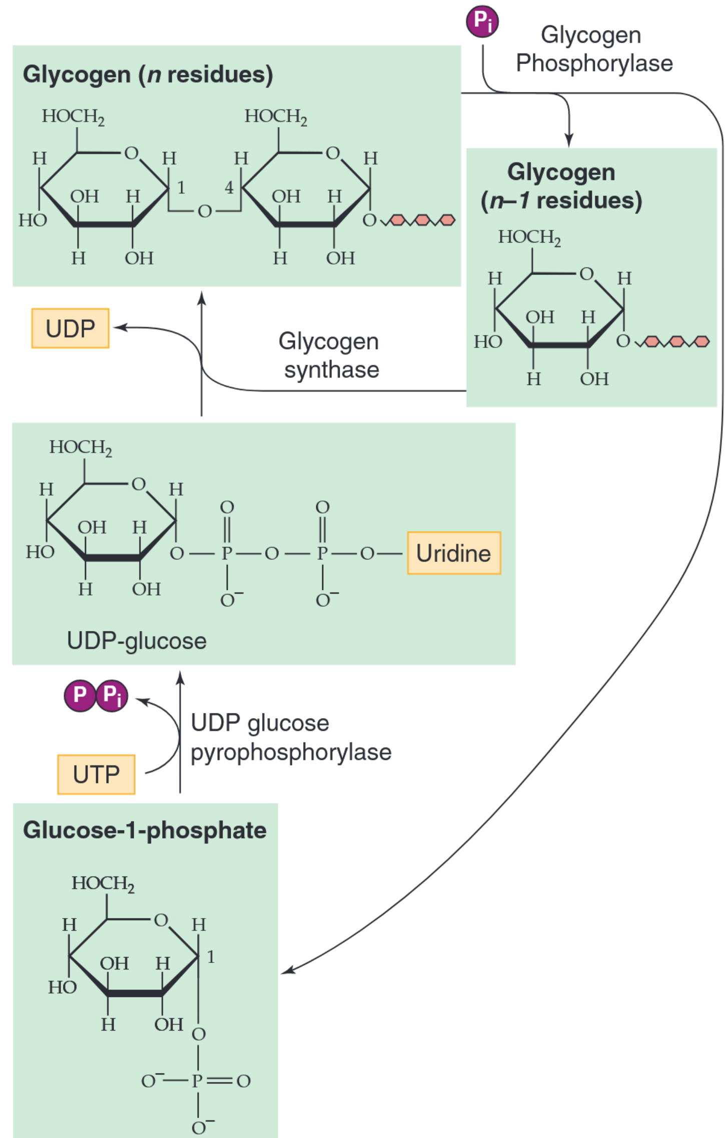
Arnold and Finley, *J Biol Chem*, 2022

Glucose can be strategically preserved in polymerized form until needed

$$\underbrace{\Delta E}_{\substack{\text{Energy of}\\ \text{ingested glucose}}} = \underbrace{\Delta G}_{\substack{\text{Energy stored}\\ \text{as glycogen}}} + \underbrace{T \cdot \Delta S}_{\substack{\text{Energy wasted}\\ \text{as heat}}}$$

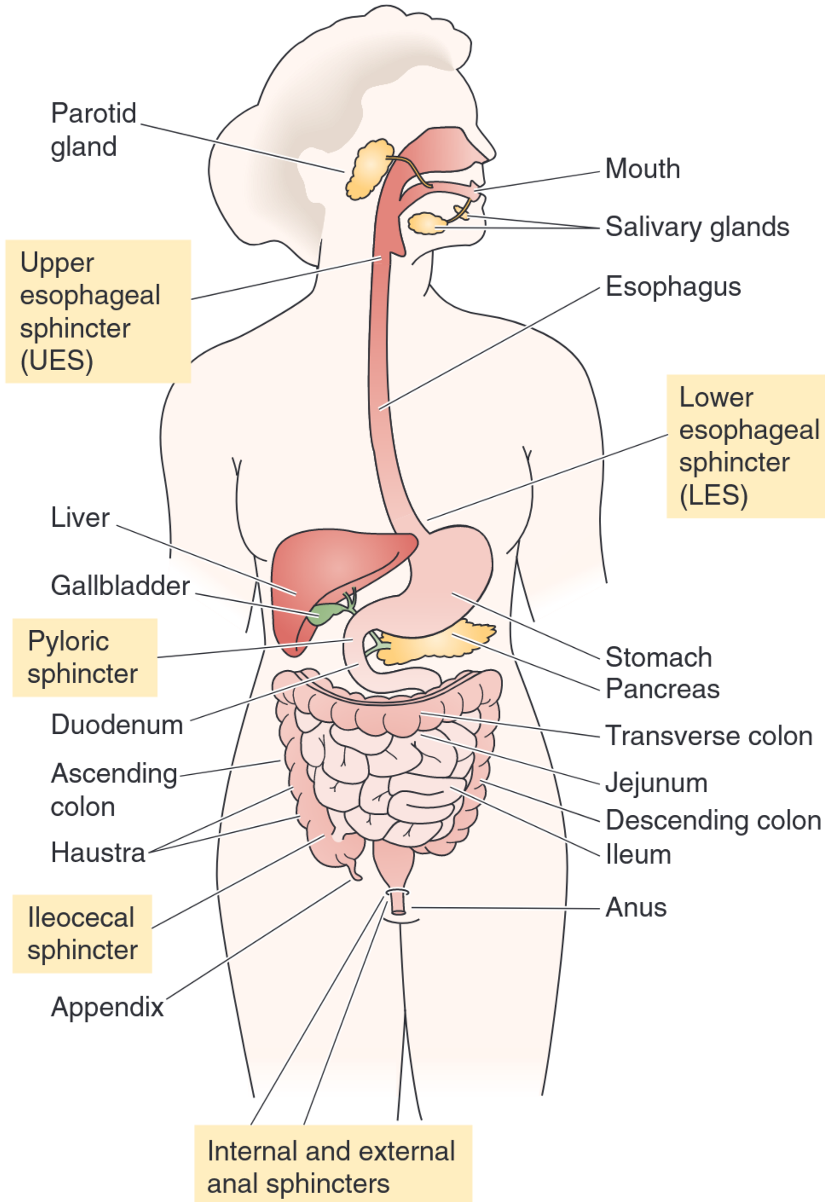
TABLE 58-1 Energy of Body Stores

CHEMICAL	WEIGHT (kg)	ENERGY DENSITY (kcal/g)	ENERGY (kcal)
Glycogen	0.7	1.5*	1,050
Protein	9.8/2 = 4.9[†]	4.3	21,000
Lipid	14	9.4	131,600



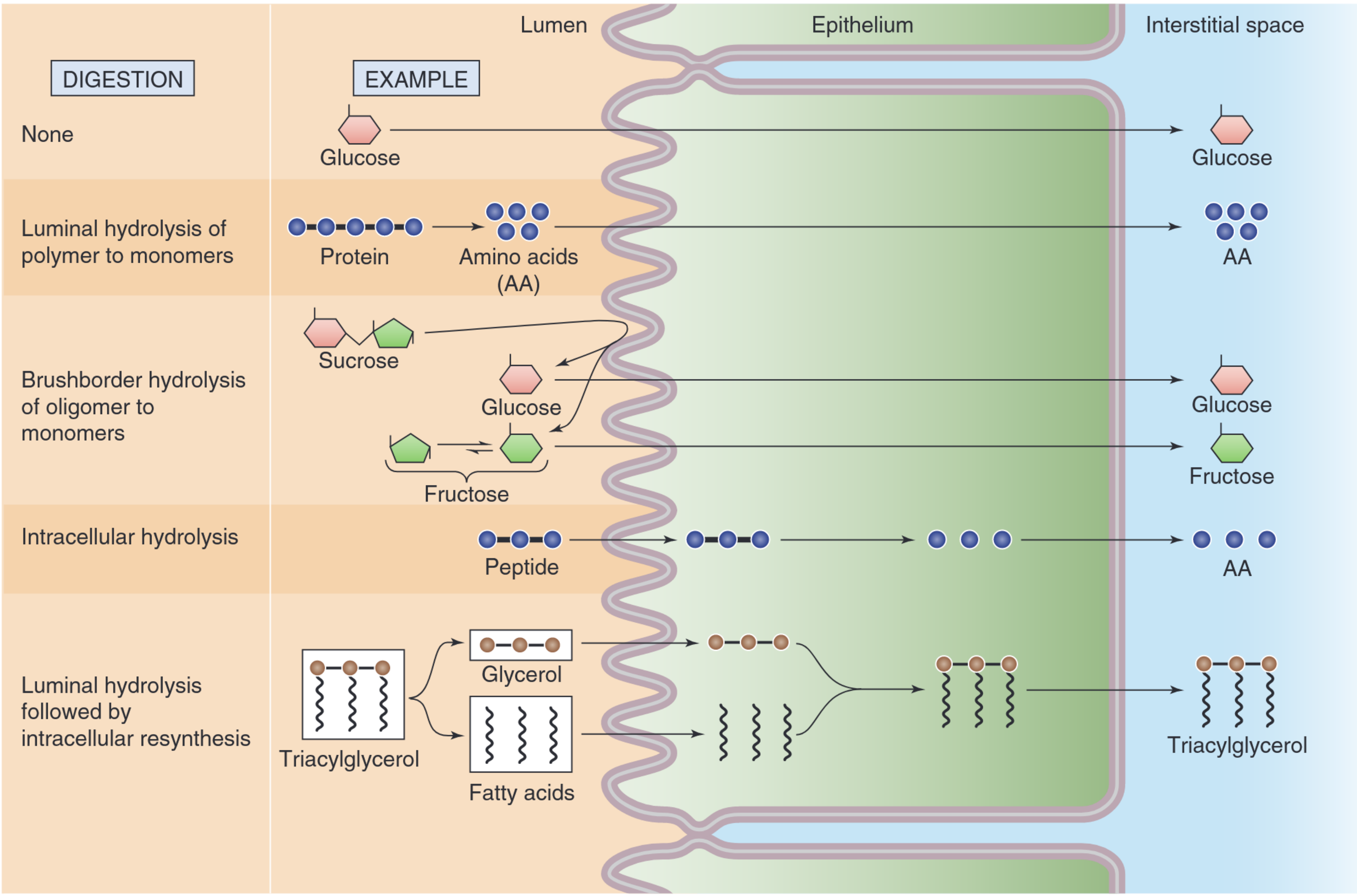
Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 58-1

Gastrointestinal tract (GI) is a machinery for energy extraction and transformation



Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 41-1

Processing of different types of nutrients in the GI tract



Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 45-1

Free glucose level in the blood is tightly regulated

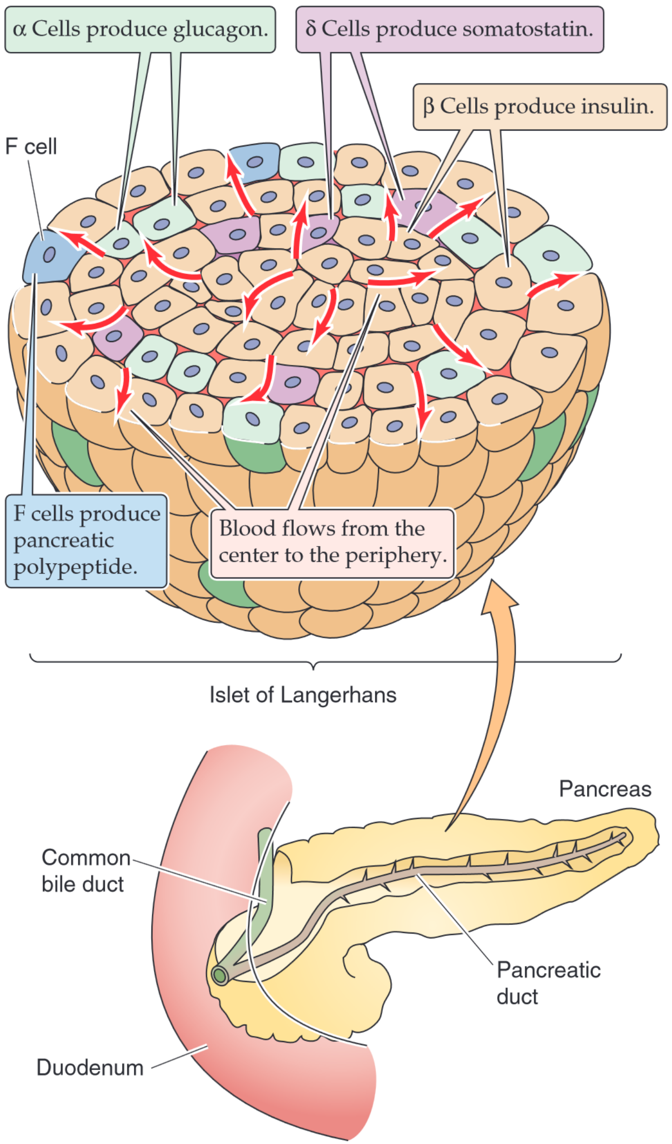


TABLE 51-2 Effects of Nutritional States

PARAMETER	AFTER A 24-hr FAST	2 hr AFTER A MIXED MEAL
Plasma [glucose], mg/dL	60–80	100–140
mM	3.3–4.4	5.6–7.8

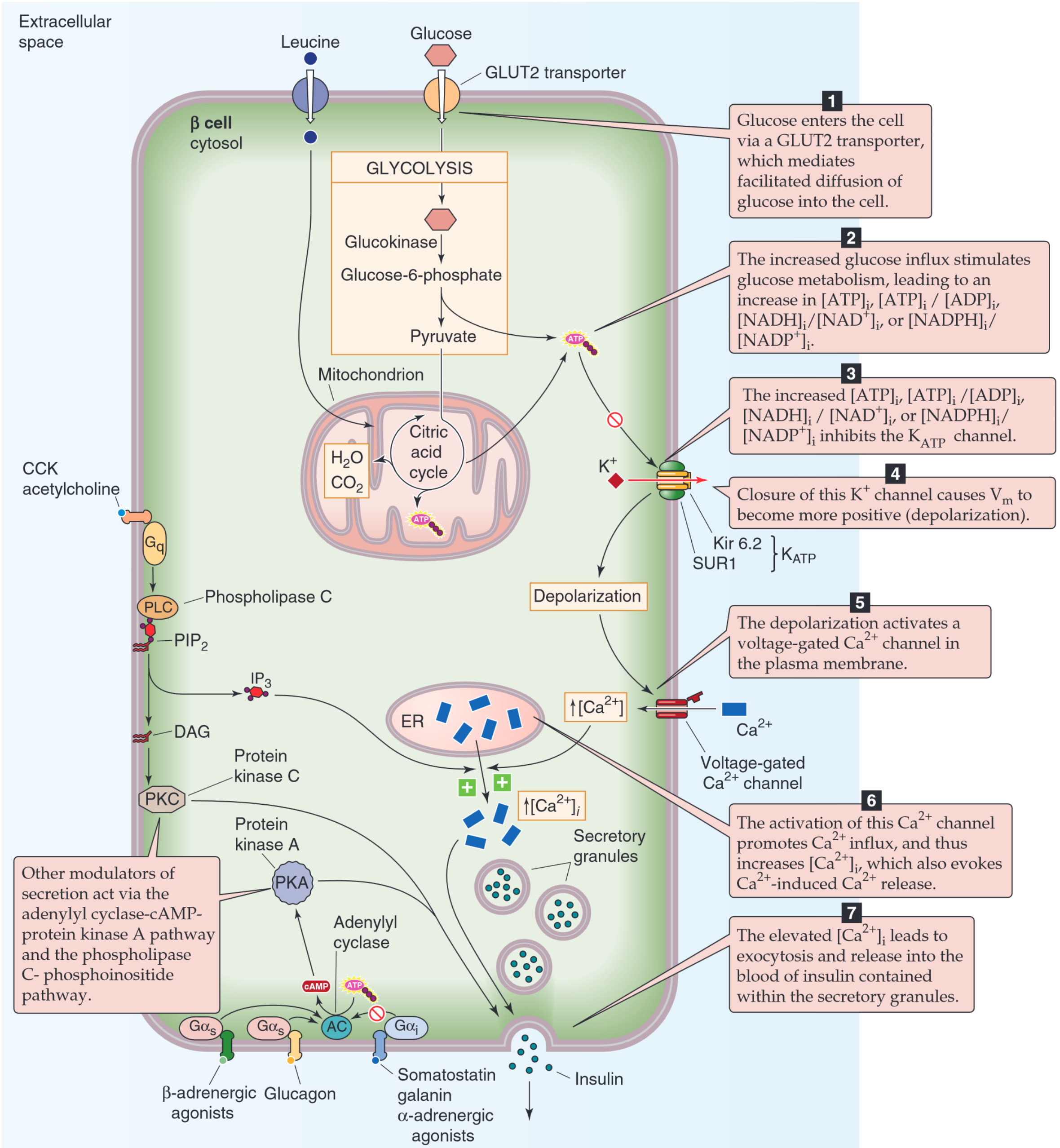
Insulin *– peptide hormone leading to:*

- *insertion of GLUT4 (insulin-dependent) glucose transporters into the plasma menbrane of muscle cells and adipocytes*
- *increase of glucose uptake into the muscles and adipocytes*
- *modulation of cellular metabolic enzymes to shift equilibrium towards utilization of free excess glucose: more glucose oxydation (ATP production), or synthesis of glycogen (muscles, liver), or lipogenesis (adipocytes)*

Glucagon *– peptide hormone with the actions opposite to insulin: hydrolysis of glycogen, increase of blood glucose*

Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 51-1

Mechanism of glucose sensing and insulin secretion in the pancreatic β-cells



Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 51-4

Dynamics of glucose metabolism

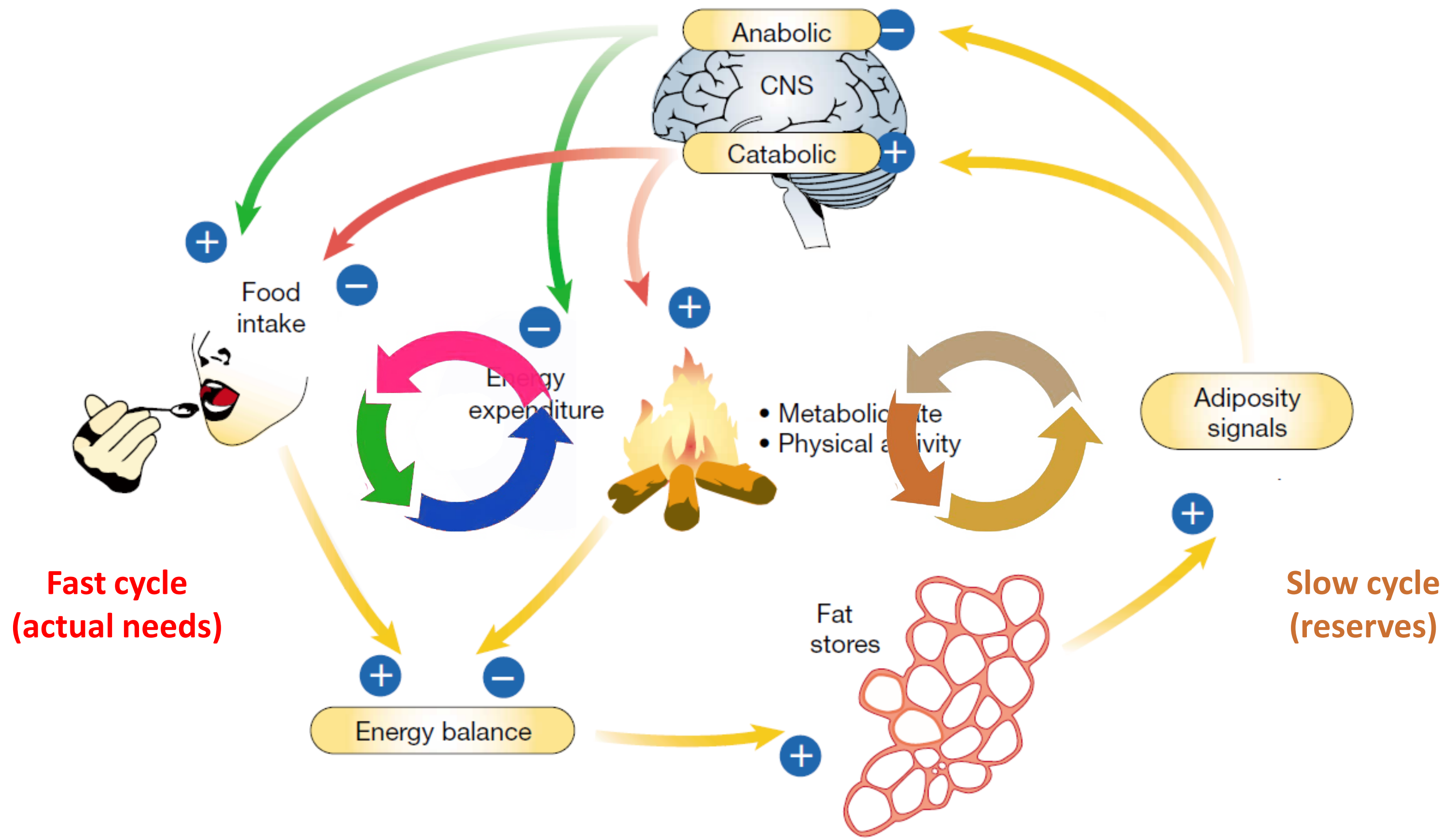
TABLE 51-2 Effects of Nutritional States

PARAMETER	AFTER A 24-hr FAST	2 hr AFTER A MIXED MEAL
Plasma [glucose], mg/dL	60–80	100–140
mM	3.3–4.4	5.6–7.8
Plasma [insulin], μU/mL	3–8	50–150
Plasma [glucagon], pg/mL	40–80	80–200
Liver	↑ Glycogenolysis ↑ Gluconeogenesis	↓ Glycogenolysis ↓ Gluconeogenesis ↑ Glycogen synthesis
Adipose tissue	Lipids mobilized for fuel	Lipids synthesized
Muscle	Lipids metabolized Protein degraded and amino acids exported	Glucose oxidized or stored as glycogen Protein preserved

Boron and Boulpaep, *Medical Physiology* 3rd ed.

Metabolic pathways in homeostasis

- **anabolic**: increased food intake, decrease of energy expenditure, glycogen synthesis, increased body fat accumulation. Example hormone: insulin
- **catabolic**: increased metabolic rate, decrease of food intake, glycogenolysis, utilisation of fat stores, decrease of body weight and fat. Example hormone: glucagon.



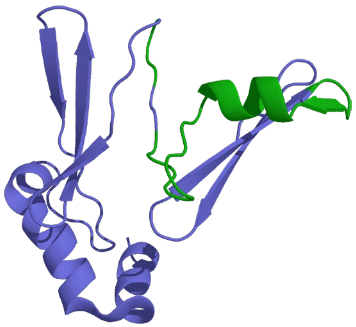
Schwartz et al., *Nature* 2000

II. Neural circuits of hunger and satiety

a) bodily signals of energy states

QUESTION: how does the body inform the brain about the energy states?

In addition to glucose and insulin, GI tract provides other hormones and sensory inputs

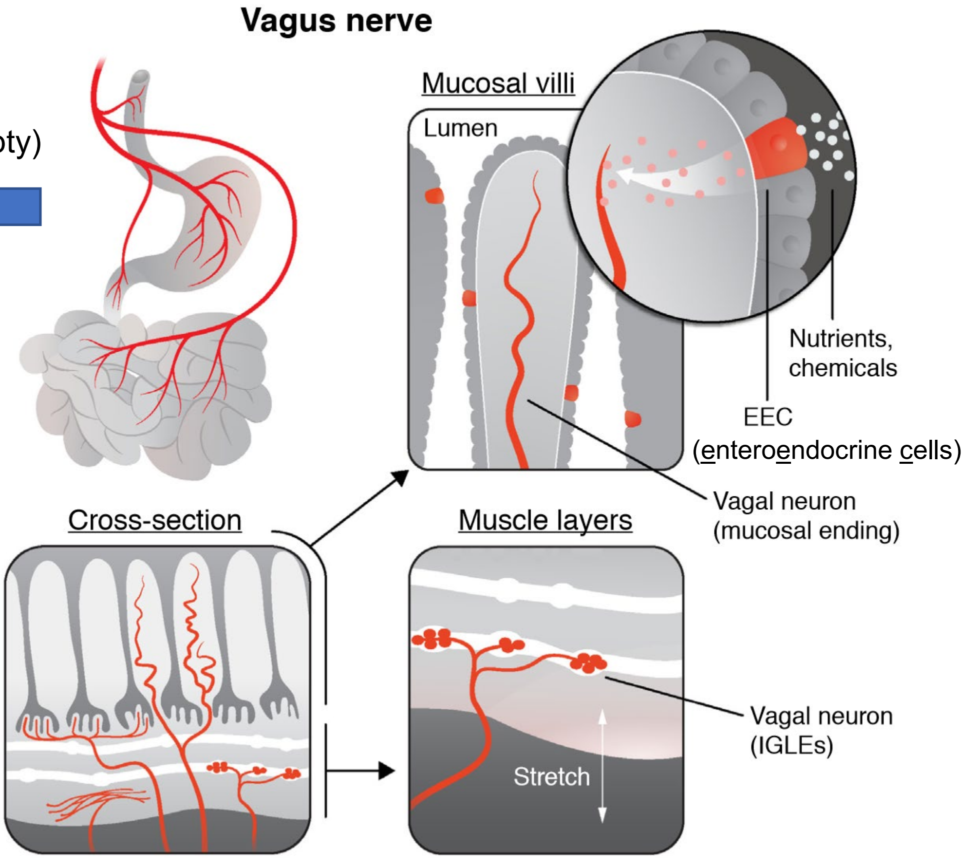


Preproghrelin (117 a.a.)
Ghrelin (28 a.a.)

a potent orexigenic factor, „hunger“ hormone

Gastric EECs (when stomach is empty)

Intestinal EECs (when food mass enters, especially fatty)



Preprocholecystokinin (150 a.a.)
CCK (58 – 8 a.a.),

an anorexigenic factor, „satiety“ hormone

Zimmerman and Knight, *Curr Opin Neurobiol* 2020

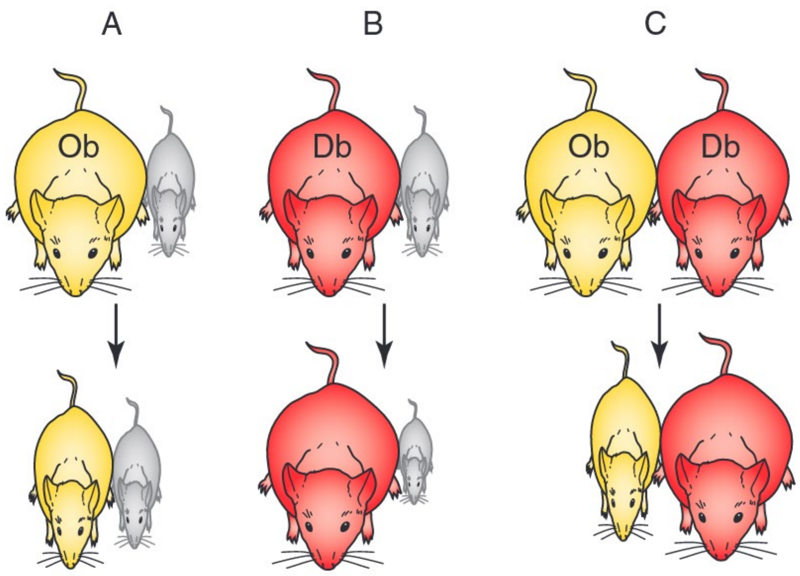
The story of leptin, an adiposity signal

ob/ob, db/db mouse (since 1950s): extremely obese, infertile diabetic mice when homozygous for ***ob*** or ***db*** genetic mutations

OB/ob and ob/ob sibling mice

Leibel, R.L., *Int J Obesity* 2008; Coleman, D., *Diabetologia* 1978

Parabiosis experiment: 1% blood circulation shared



A = Ob mouse + Wt mouse
B = Db mouse + Wt mouse
C = Ob mouse + Db mouse

Boron and Boulpaep, *Medical Physiology* 3rd ed.: Fig. 48-8

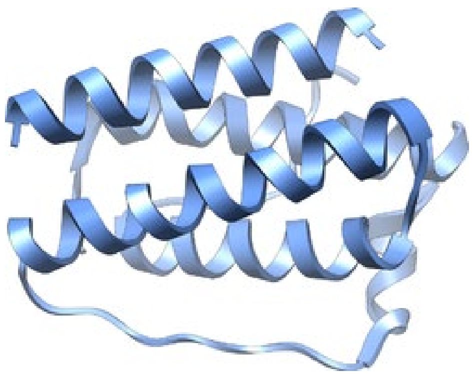
Parabiosis results:

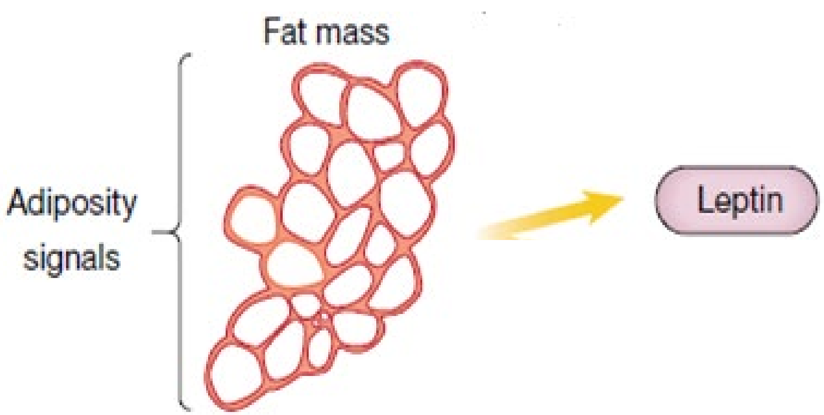
⇒ ***ob* gene product is a soluble factor signaling satiety**

⇒ ***db* gene product is receptor for the *ob*-linked soluble factor**

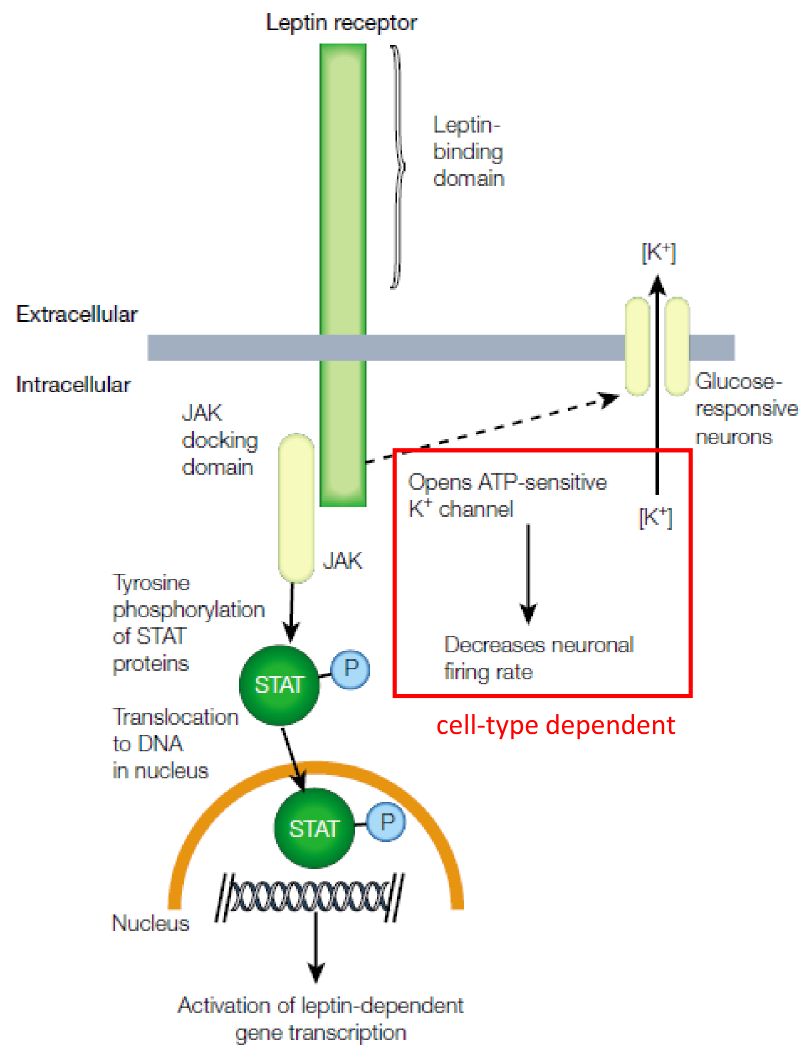
The story of leptin, an adiposity signal

ob **gene product: leptin (167 a.a.)**





db **gene product: leptin receptor**



Schwartz et al., *Nature* 2000

The story of leptin, an adiposity signal

<u>**Hyperphagia**</u>
feeling hungry, strong appetite, high food intake

age: 3 years
weight: 42 kg

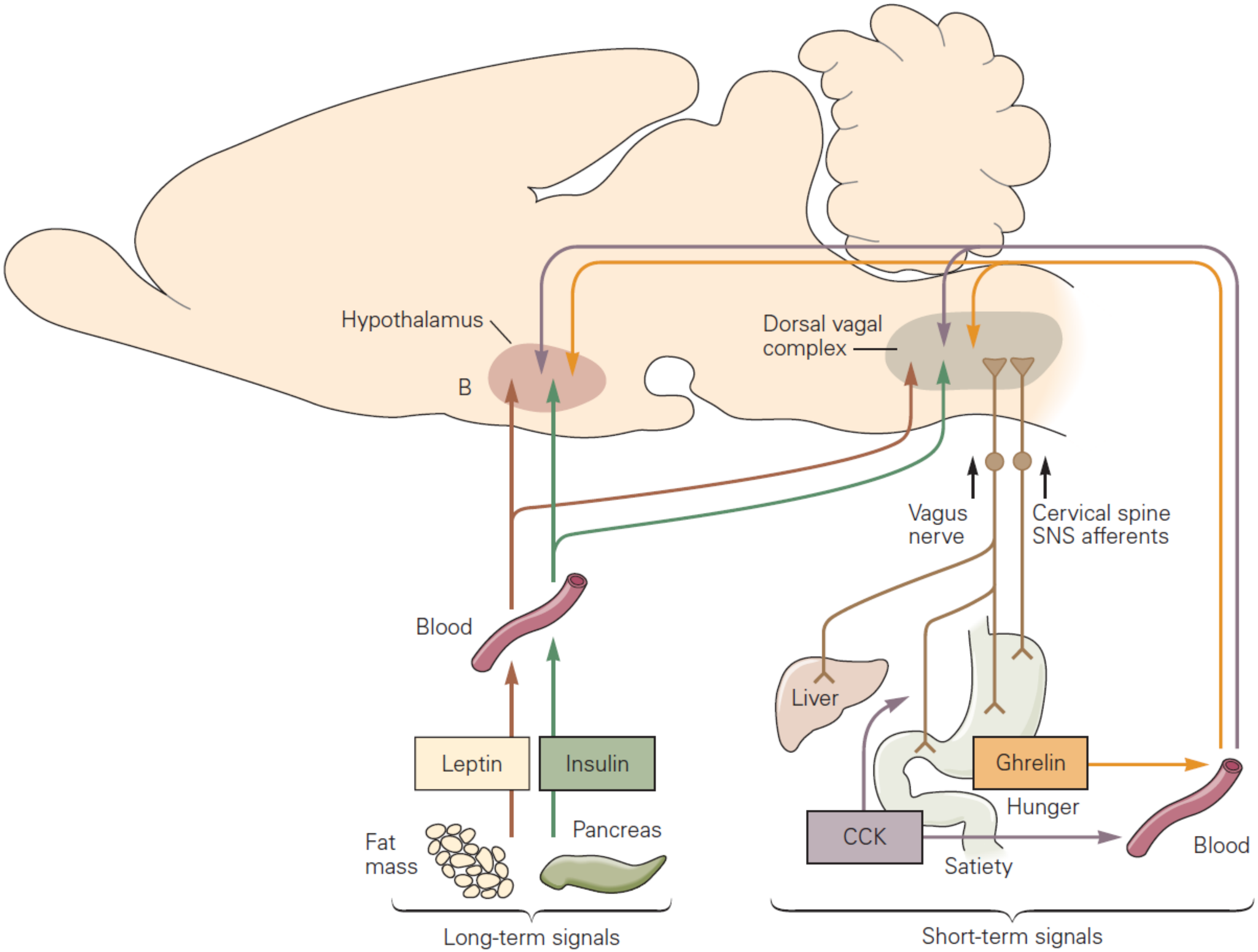
age: 7 years
weight: 32 kg

(after leptin therapy)

<u>leptin is an **anorexigenic** peptide</u>
(„orexis“ from Greek is appetite)

Neuroscience, 5th ed. by D. Purves – Box 21C

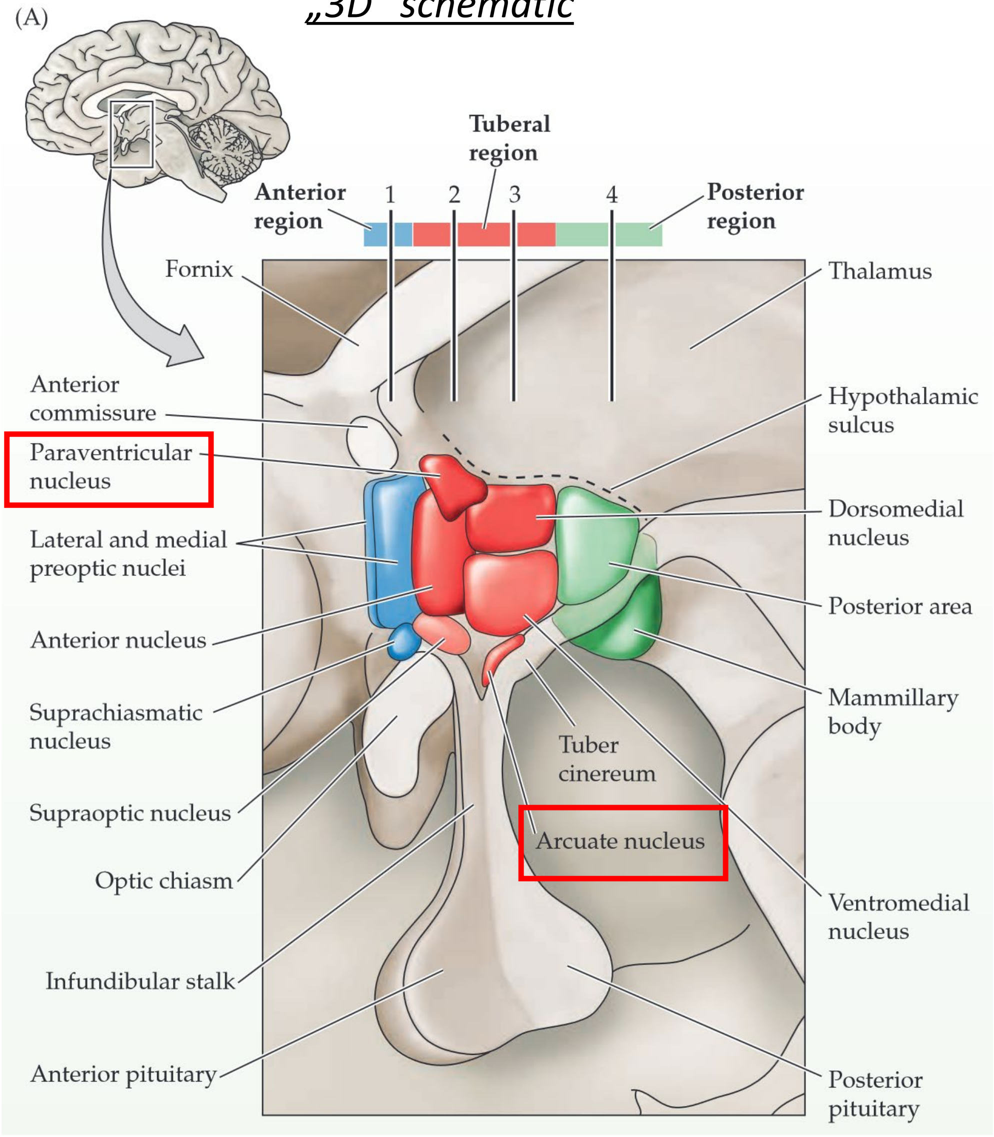
General overview schematic of the feeding control system



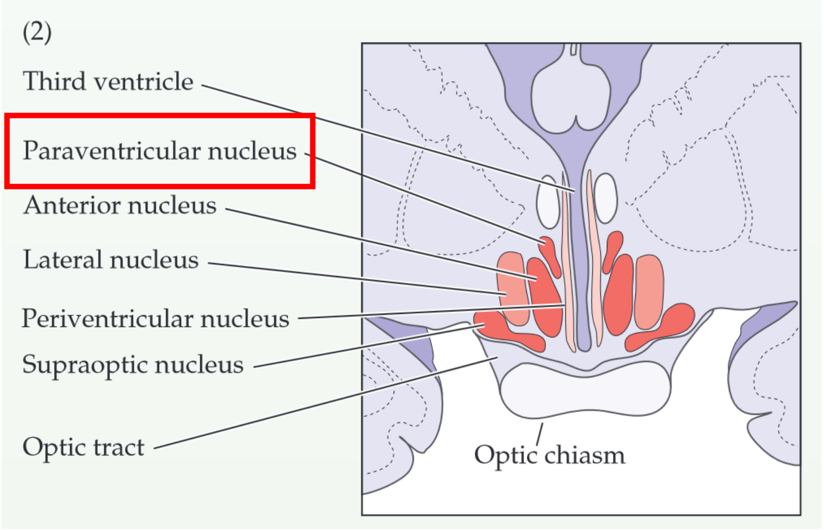
Kandel, *Principles of Neural Science, 5th ed.,* Fig. 49-3

Hypothalamic nuclei central to feeding control: ARC and PVH

„3D“ schematic



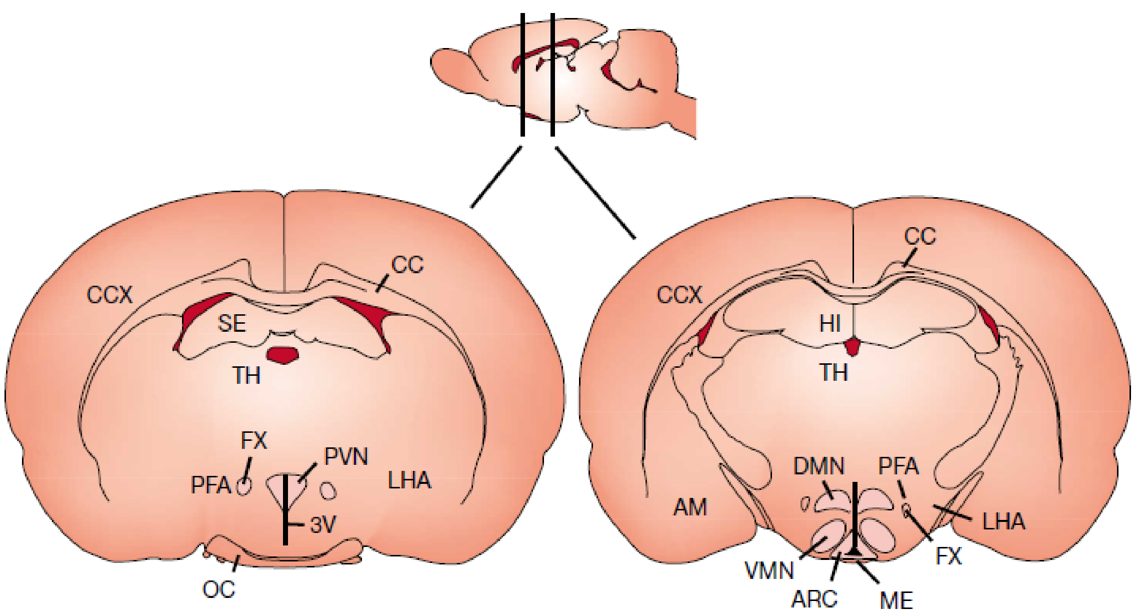
Human brain, coronal section

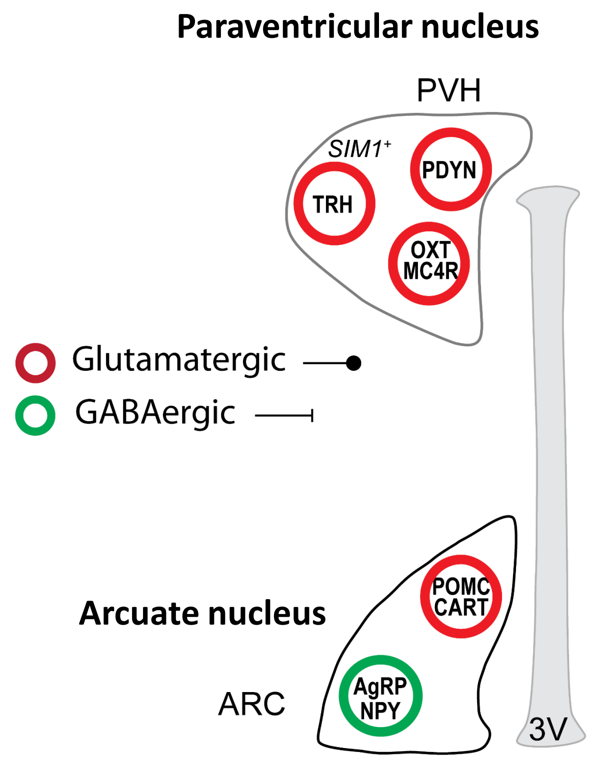


Purves 6th Ed., *Box 21A*

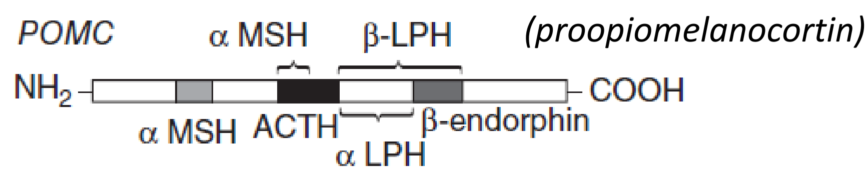
Hypothalamic nuclei central to feeding control: ARC and PVH

<u>*Mouse brain, coronal section*</u>





<u>Key for molecules</u>:
POMC: proopiomelanocortin
CART: cocaine-amphetamine-related transcript
AgRP: agouti-related protein
NPY: neuropeptide Y
OXT: oxytocin
MC4R: MC4 receptor for αMSH (melanocortin receptor)
αMSH: melanocyte stimulating hormone
TRH: thyrotropin-releasing hormone
ACTH: corticotropin
PDYN: prodynorphin

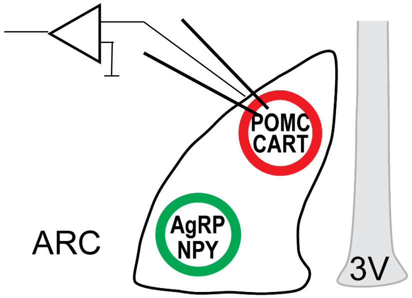


II. Neural circuits of hunger and satiety

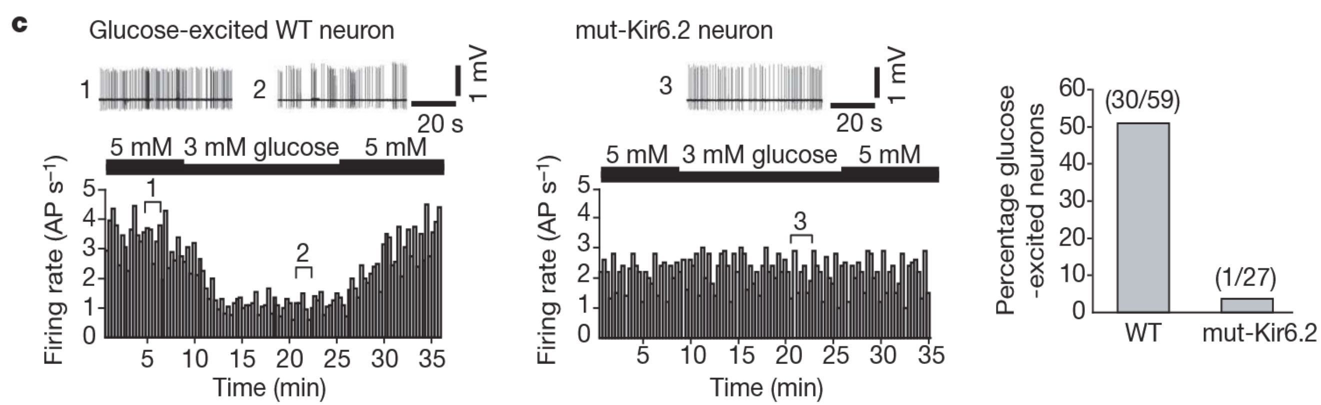
b) sensing of satiety / hunger signals by POMC and AgRP neurons

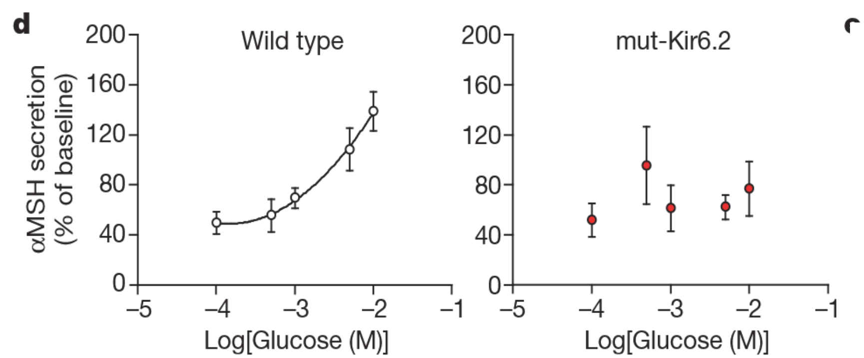
QUESTION: how does the brain know about body energy state?

POMC neurons in ARC sense glucose concentration (inhibited by lowering glucose)



Mice: POMC-GFP (WT) *or* POMC-mutated Kir6.2 ATP-sensitive K-channels
(see slide #12 for glucose sensing in islet β-cells: the same mechanism!)



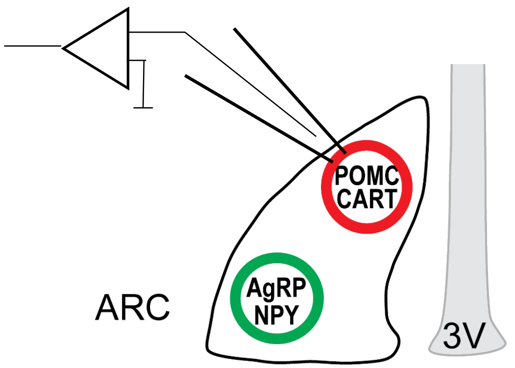


Parton et al., *Nature, 2007*

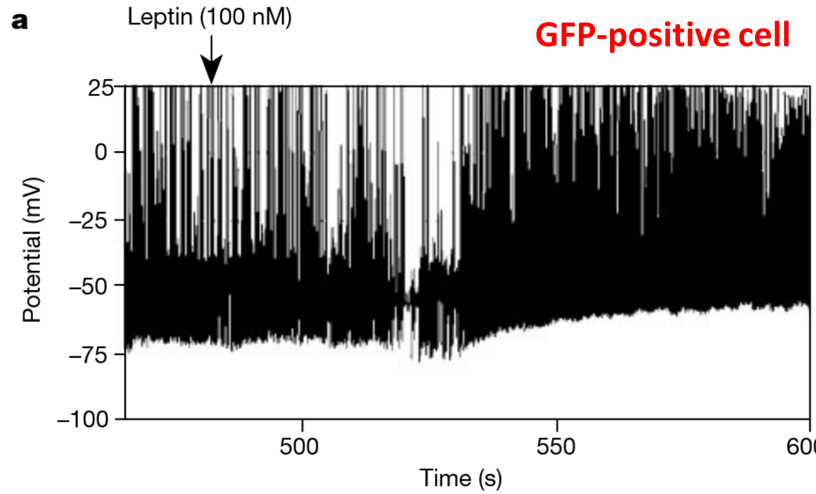
⇒ POMC neurons in ARC directly sense glucose concentration (excited by glucose)
⇒ Mechanism of glucose sensitivity is similar to one in insulin secreting pancreatic β-cells

POMC neurons in ARC are depolarized by adiposity signal (leptin)

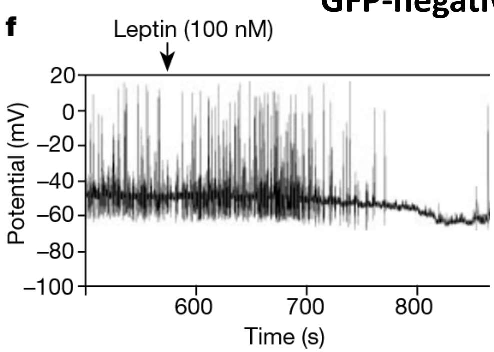
Mice: <u>POMC-GFP</u>

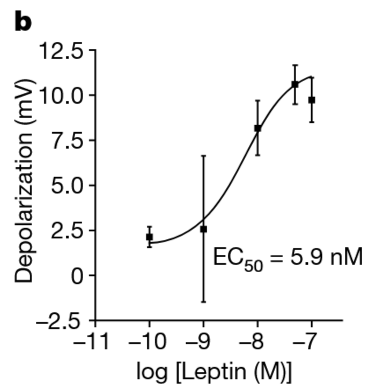


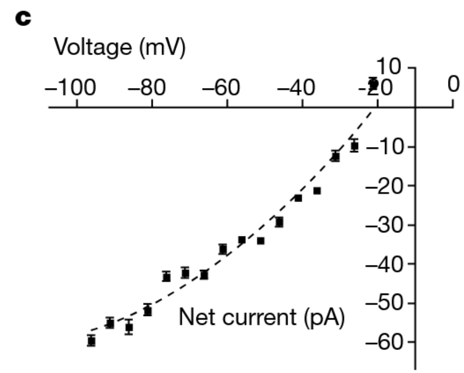
GFP-positive cell



GFP-negative cell







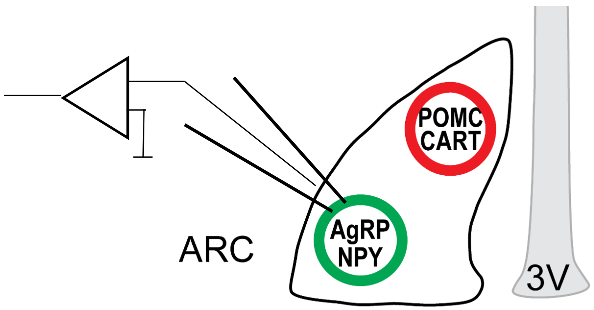
Cowley et al., *Nature,* 2001

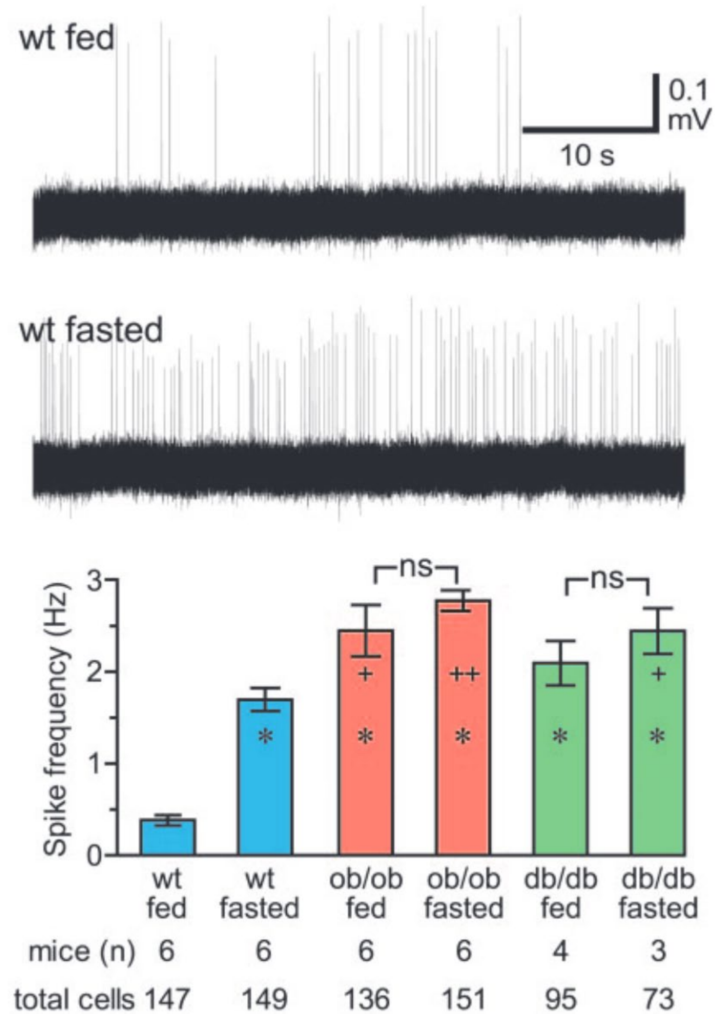
⇒ **POMC neurons in ARC are depolarized by direct leptin application**

⇒ **Not a „typical“ leptin response (see slide 18); here works via non-specific depolarizing channels**

AgRP neurons in ARC are more active at low energy (fasted) state

Mice: NPY-sapphire reporter





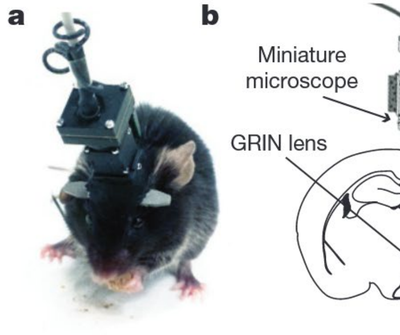
Takahashi and Cone, *Endocrinology, 2005*

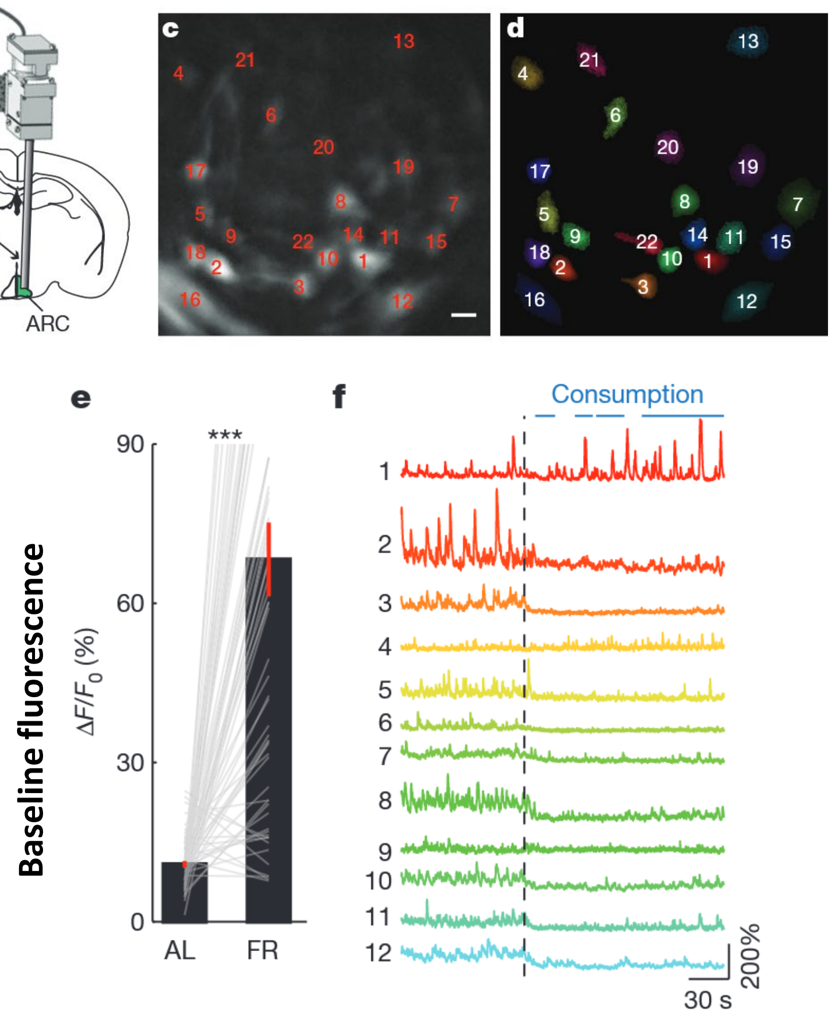
See slide 18!
Here, the effect of leptin is „typical“
hyperpolarizing, likely via opening K-channels

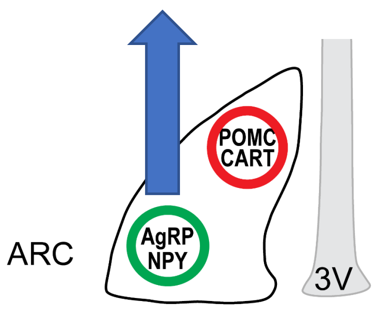
⇒ **Baseline firing of AgRP/NPY neurons is higher in fasted then in fed mice**
⇒ **This is dependent on intact leptin signaling and is removed by i.p. leptin injection**

AgRP neurons in ARC are more active at low energy (fasted) state

Mice: AgRP-ires-Cre, injected Cre-dependent GCaMP6 vector into ARC



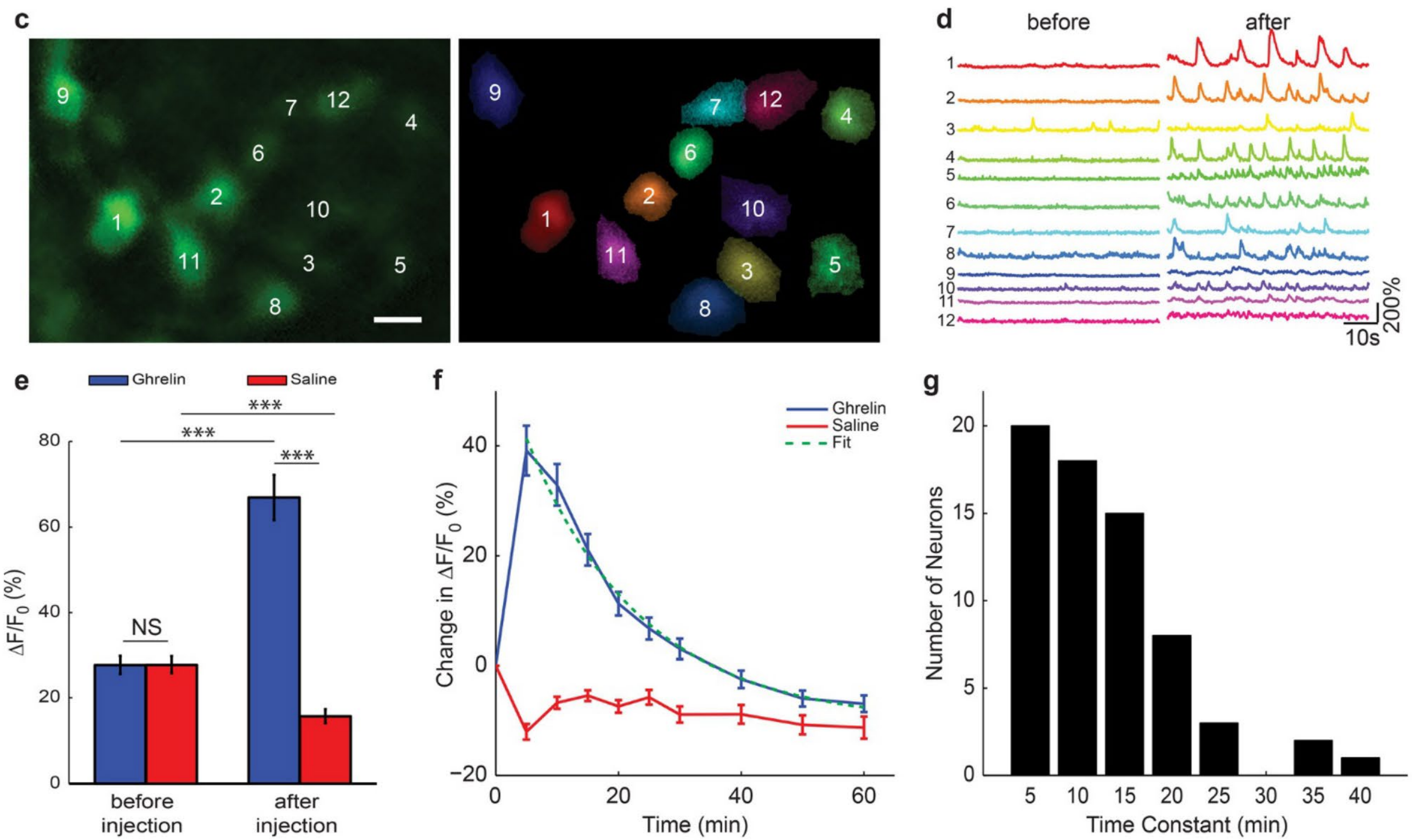




Betley et al., *Nature, 2015*

⇒ **In-vivo imaging confirms increased firing frequency in ARC AgRP neurons after food-restricted mice (FR) vs *ad libitum* fed (AL) mice**

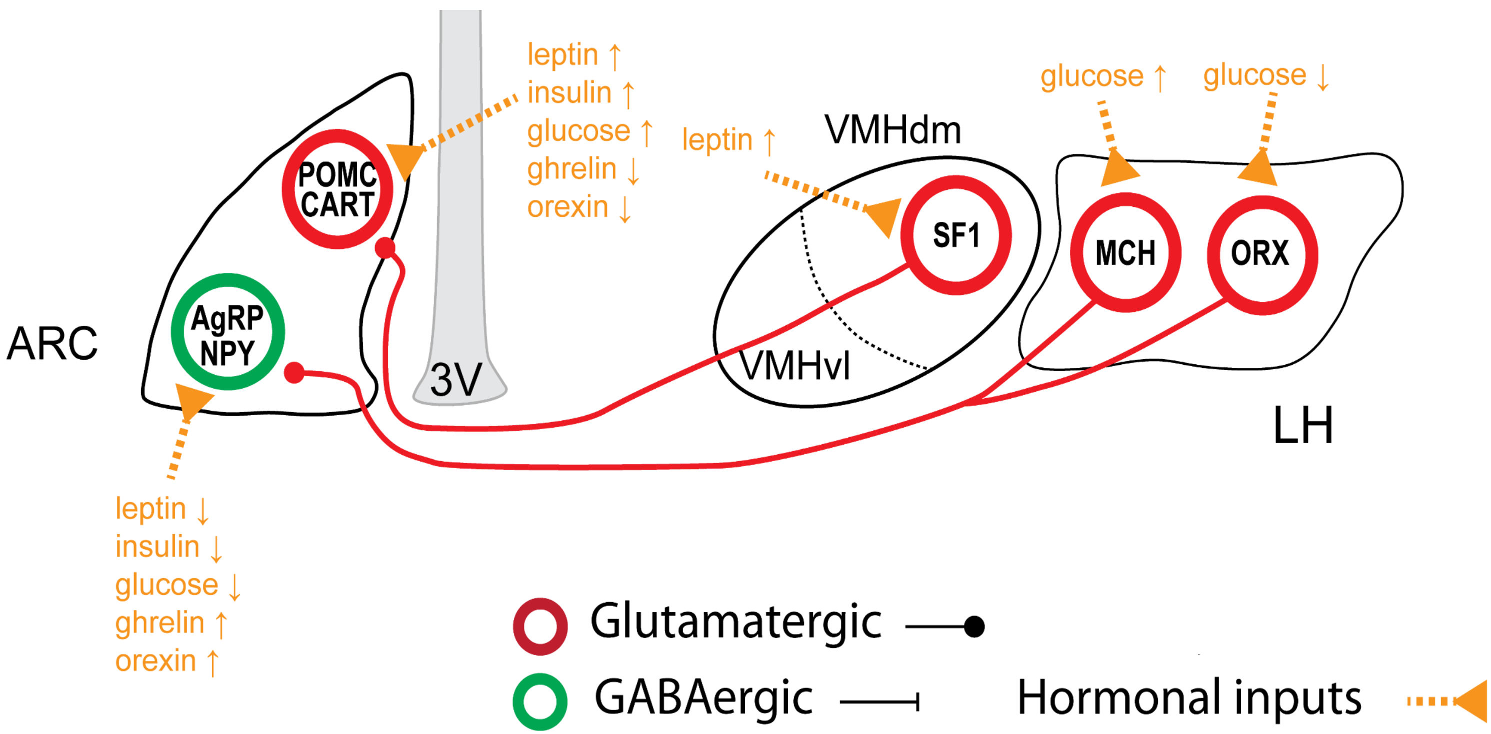
AgRP neurons in ARC are directly activated by low energy signal (ghrelin)



Betley et al., *Nature, 2015*

⇒ In fed mice, ARC AgRP activity increases after i.p. ghrelin injection (1 μg/g body weight)

External signals of the energy states from outside of the ARC nucleus

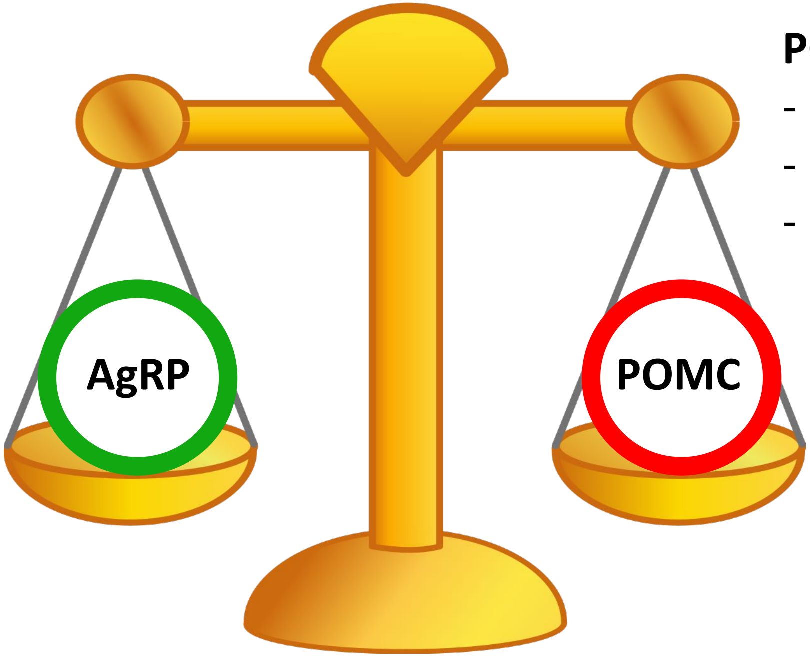


⇒ **ARC neurons also receive external inputs from glucose and leptin-sensitive neurons**

Summary: opposite functions of the AgRP and POMC ARC neurons in feeding control

AgRP respond to: *hunger*

- food restriction ↑
- Ghrelin ↑
- Leptin ↓
- food intake ↓
- …



POMC respond to: *satiety*

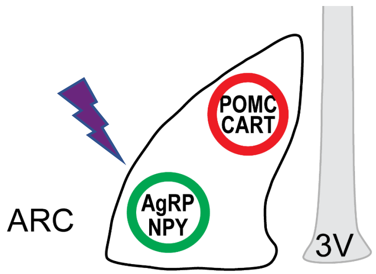
- Glucose ↑
- Leptin ↑
- …

II. Neural circuits of hunger and satiety

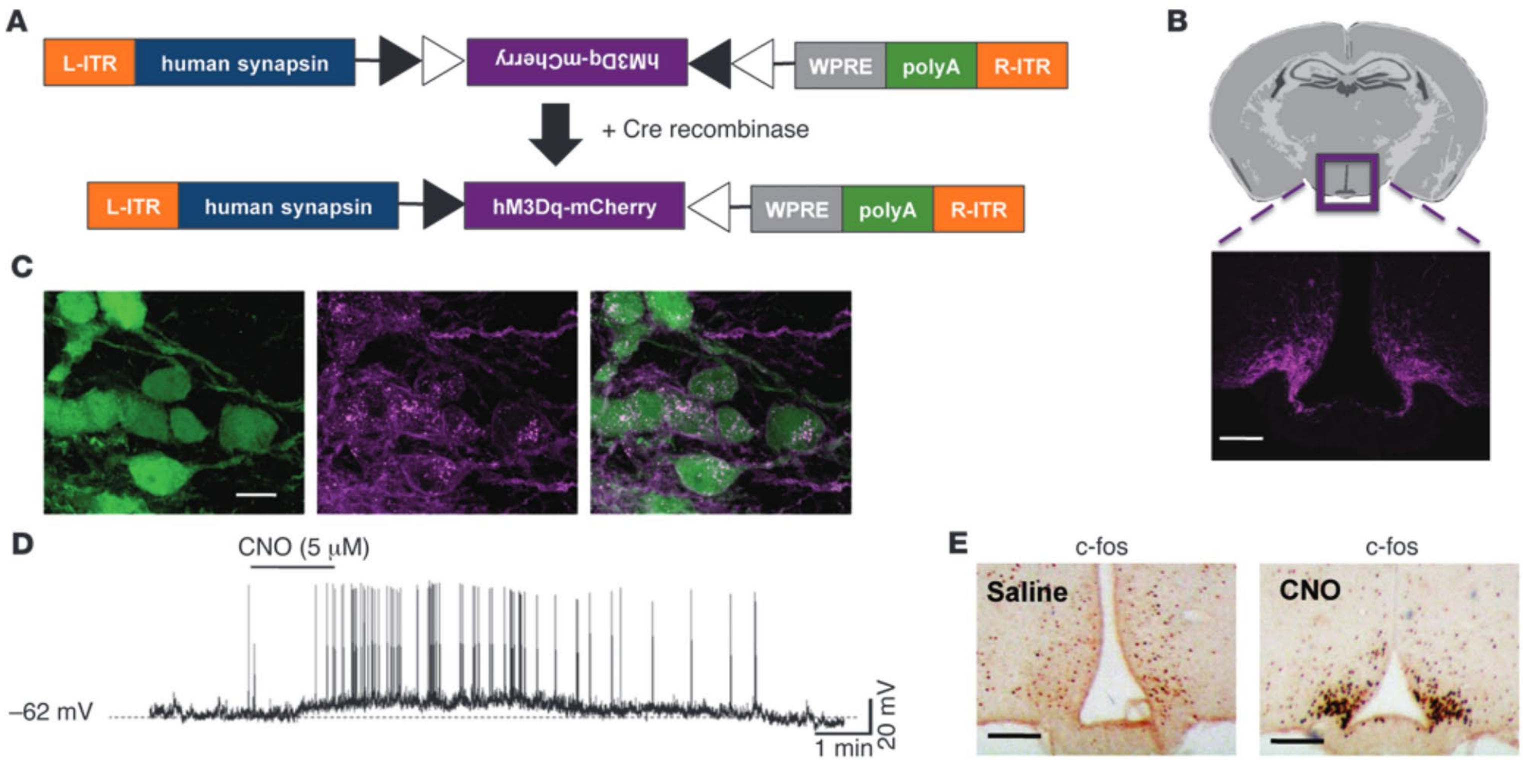
c) balancing function of the ARC (the arcuate nucleus)

QUESTION: do these energy state-sensitive neurons control feeding?

Testing the role of AgRP neurons in ARC: chemogenetic <u>stimulation</u> using DREADDs

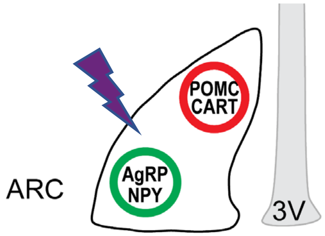


Mice: AgRP-*ires*-Cre



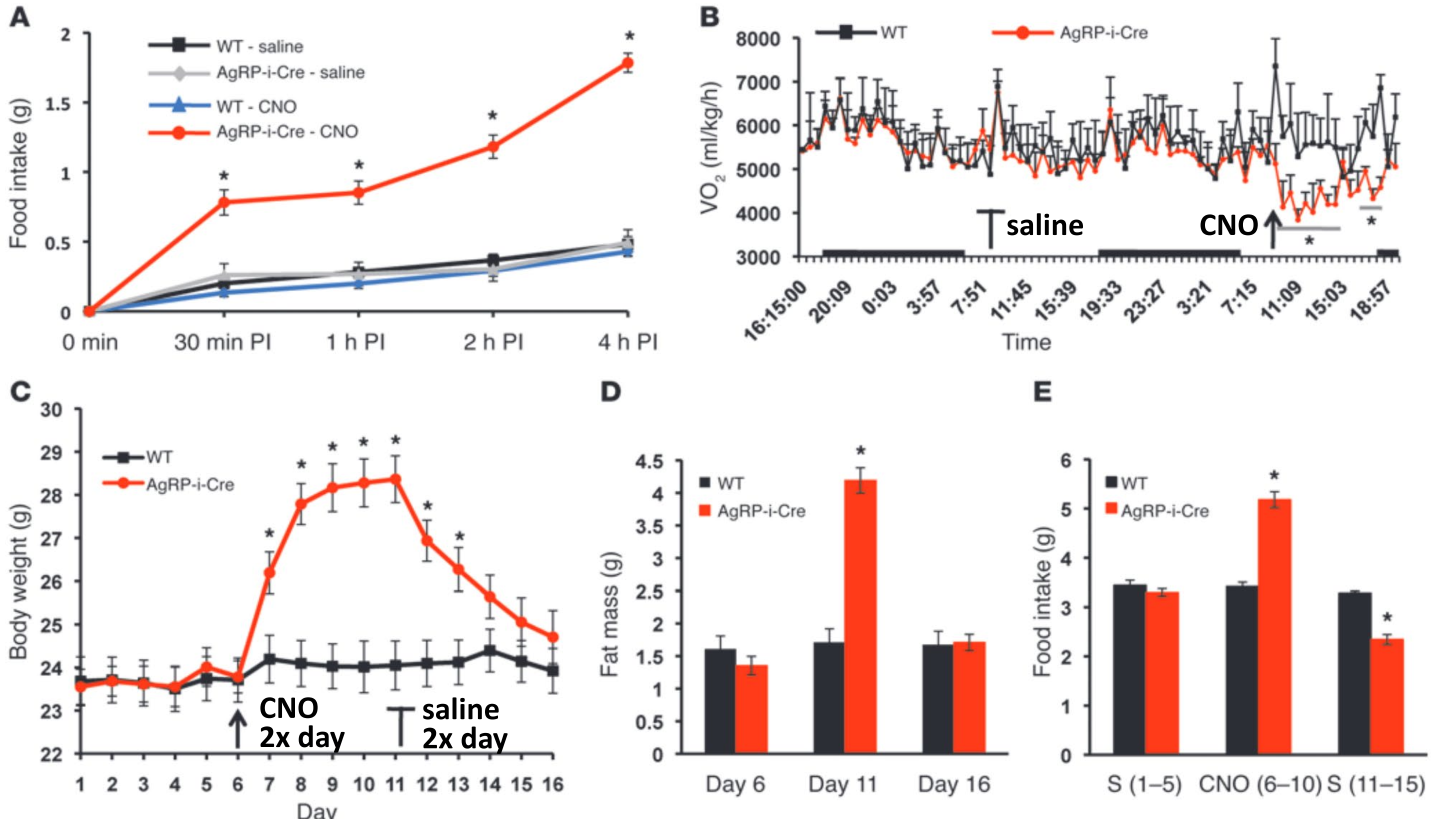
Krashes et al., *J Clin Invest, 2011*

Testing the role of AgRP neurons in ARC: chemogenetic <u>stimulation</u> using DREADDs



Mice: AgRP-*ires*-Cre

O_2 consumption in volumetric cages

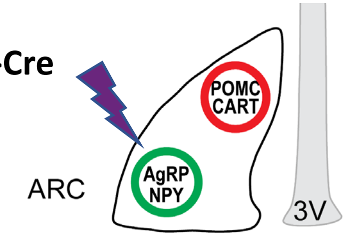


Krashes et al., *J Clin Invest, 2011*

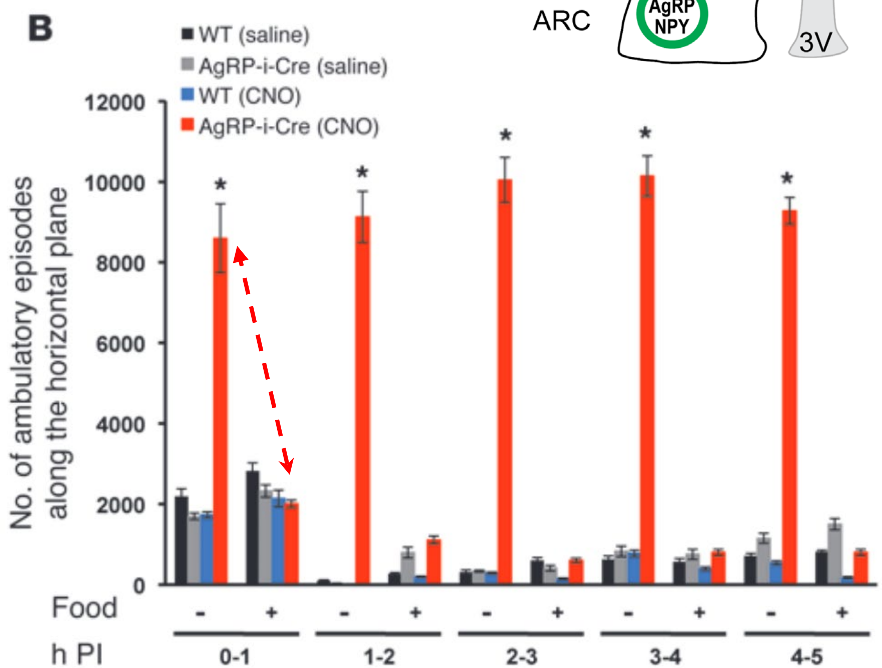
- ⇒ **Acute chemogenetic stimulation of AgRP neurons stimulates eating in fed mice**
- ⇒ **Also, it acutely stimulates anabolic regime (reduced O_2 consumption)**
- ⇒ **Chronic stimulation leads to a remarkable but reversible weight gain (fat mass)**

Testing the role of AgRP neurons in ARC: chemogenetic <u>stimulation</u> using DREADDs

Mice: AgRP-*ires*-Cre



Ad libitum food was removed after CNO injection

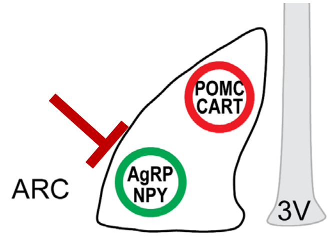


Krashes et al., *J Clin Invest, 2011*

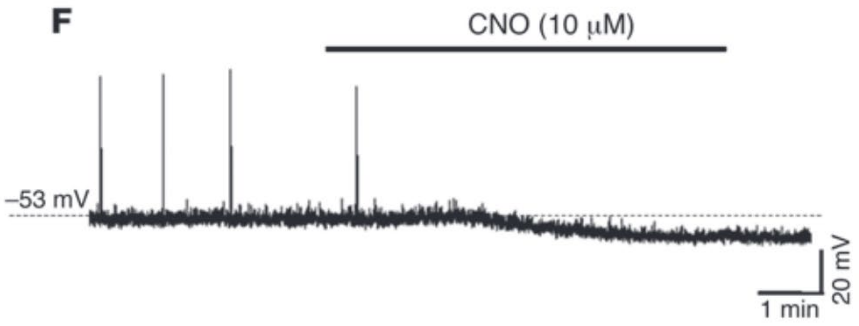
⇒ **Acute stimulation of AgRP neurons stimulated mobility only if food was absent (foraging?)**

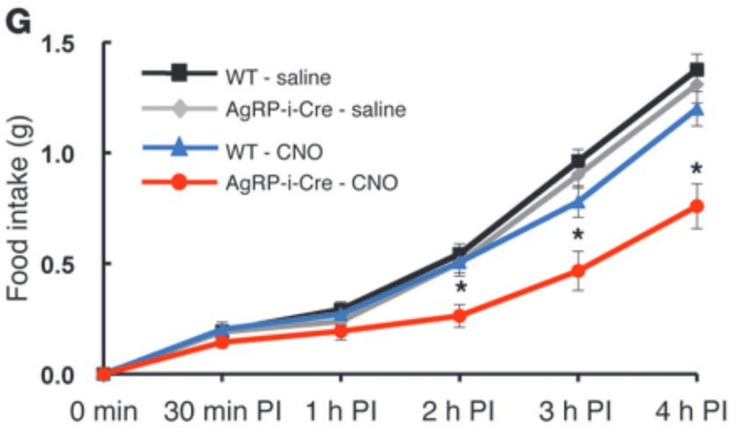
Testing the role of AgRP neurons in ARC: chemogenetic <u>inhibition</u> using DREADDs

Mice: AgRP-*ires*-Cre; hM4Di in ARC



Slice patch recording for confirmation

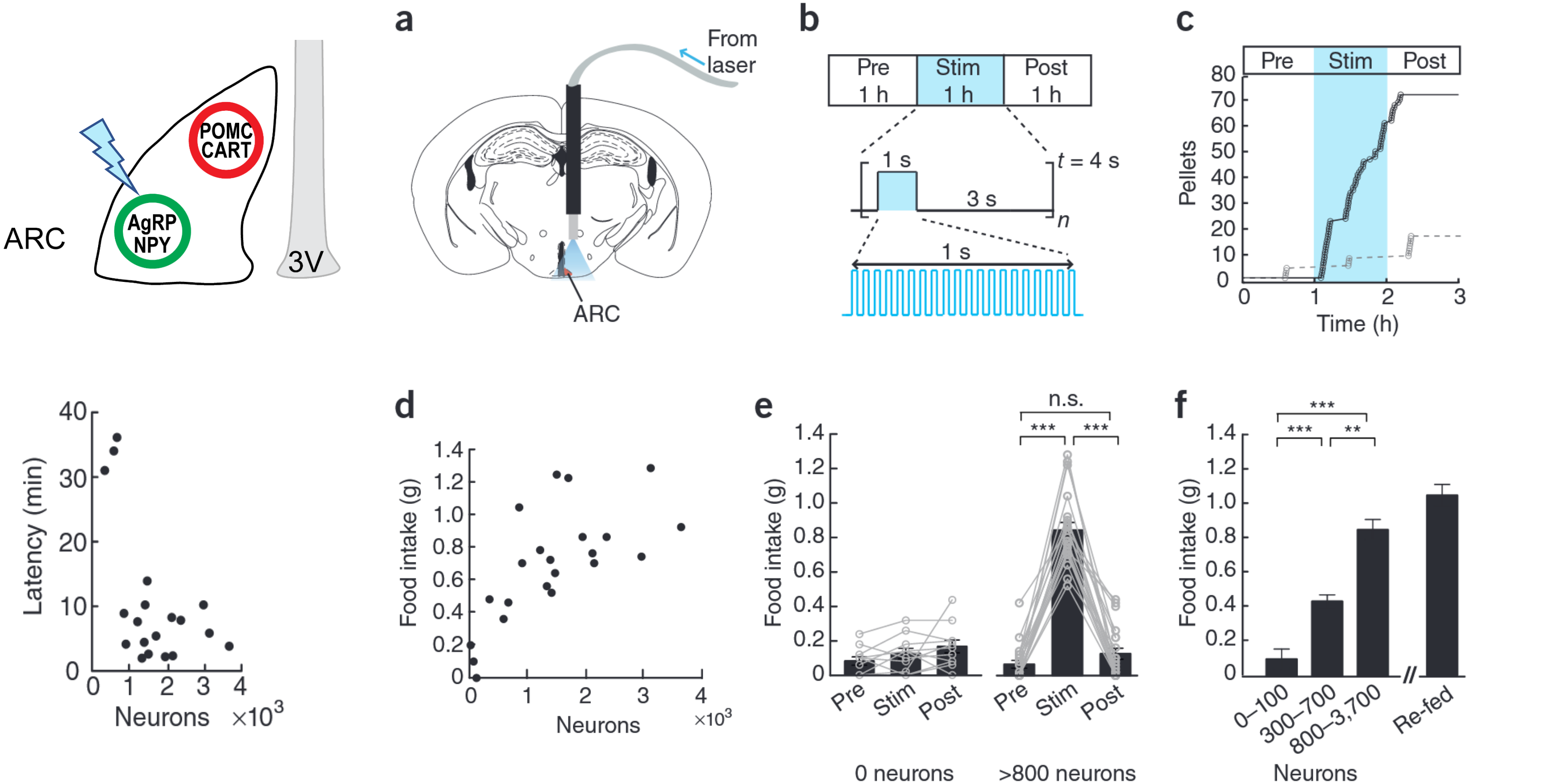




⇒ **Conversely, acute chemogenetic inhibition of AgRP neurons reduced feeding for hours**

Testing the role of AgRP neurons in ARC: optogenetic <u>stimulation</u> using ChR2

Mice: AgRP-*ires*-Cre
AAV : FLEX : ChR2-tdTomato



Aponte et al., *Nat Neurosci, 2011*

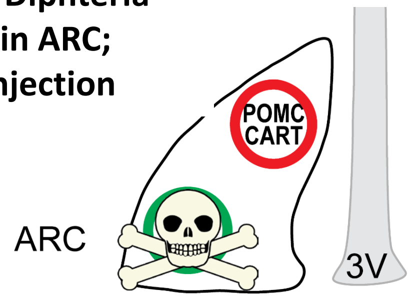
⇒ **Optogenetic stimulation of AgRP neurons stimulates voracious food intake within minutes**

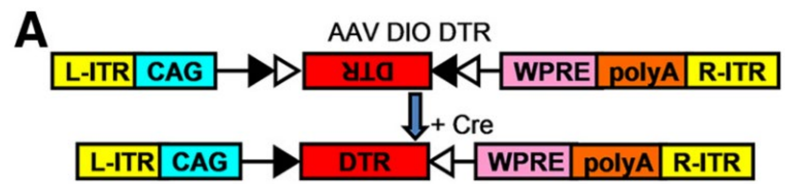
⇒ **This behavior dose-depended on the number of stimulated neurons in ARC**

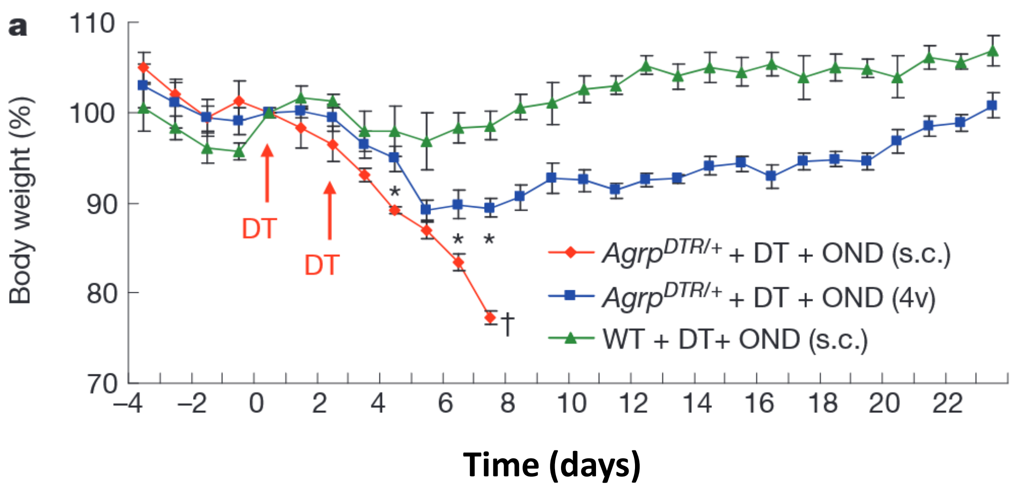
⇒ **In line with chemogenetic results above, AgRP neurons in ARC are orexigenic**

Testing the role of AgRP neurons in ARC: genetic ablation experiment

Mice: AgRP-ires-Cre; Diphteria toxin receptor (DTR) in ARC; DT whole-body i.p. injection



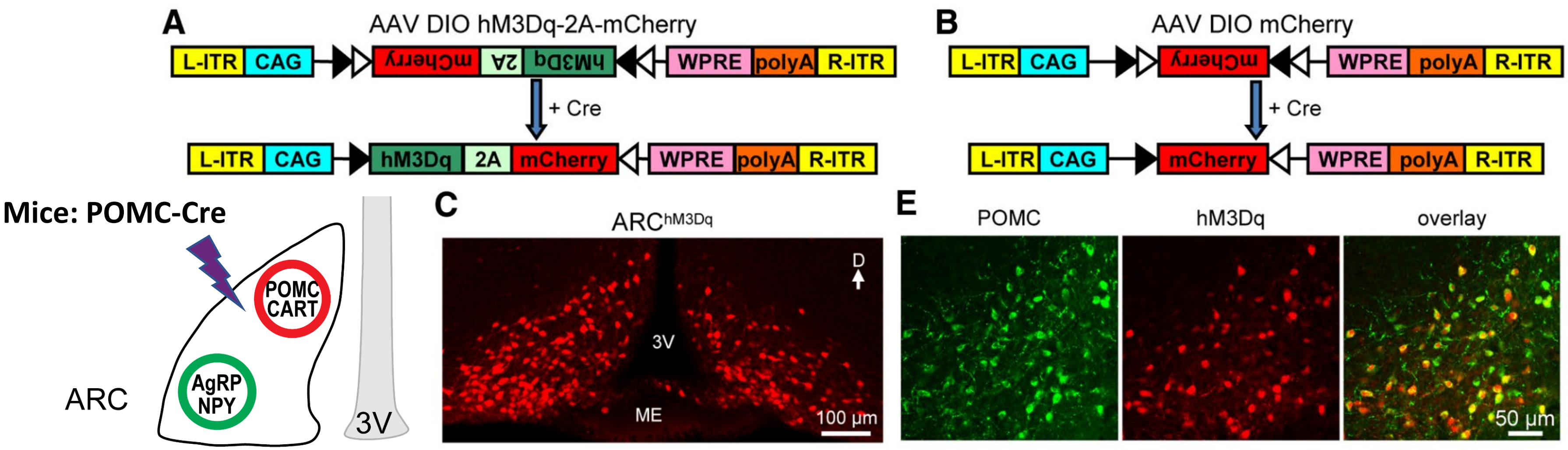


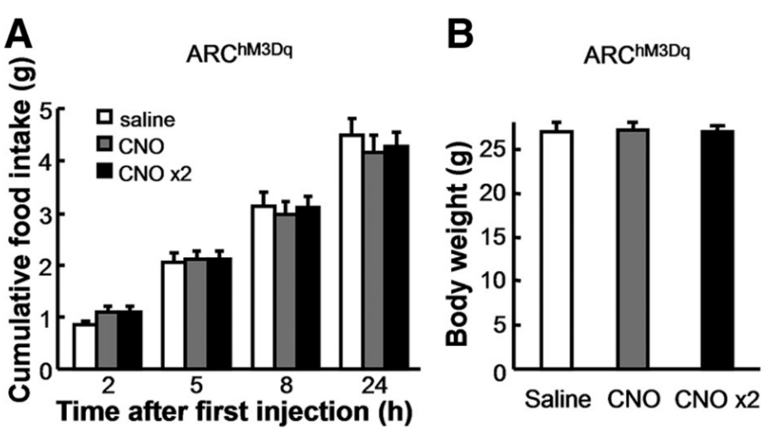


Wu et al., *Nature, 2012*

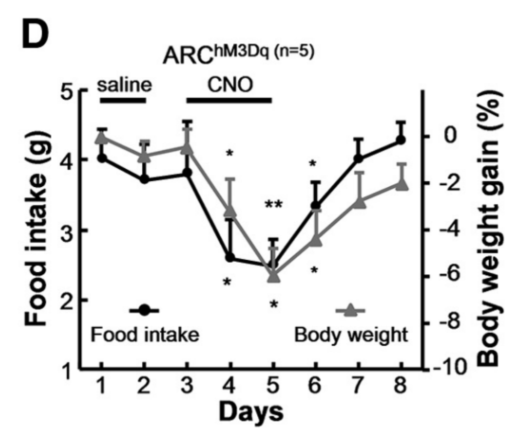
⇒ In contrast, ablation of AgRP neurons stops food intake, leads to weight loss and death

Testing the role of POMC neurons in ARC: chemogenetic stimulation using DREADDs





no immediate,
but chronic effect

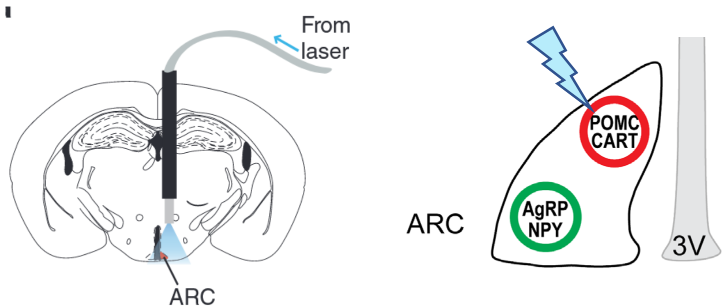


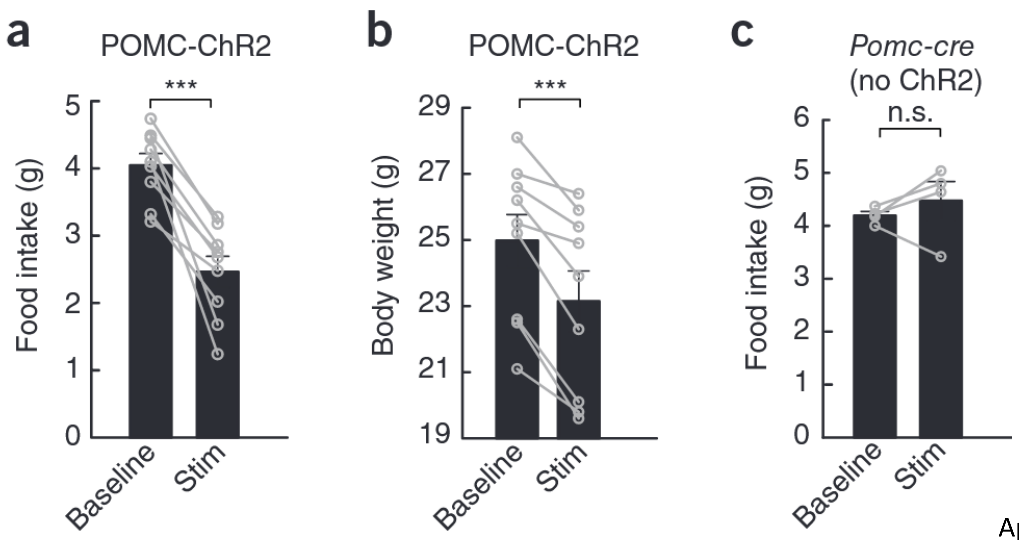
Zhan, Zhou et al., *J Neurosci, 2013*

⇒ **Chronic (>3 days) chemogenetic stimulation of POMC neurons in ARC is anorexigenic**

Testing the role of POMC neurons in ARC: optogenetic <u>stimulation</u> using ChR2

Mice: POMC-*ires*-Cre
AAV:FLEX:ChR2-tdTomato (optostimulation <u>for 24 h!</u>)



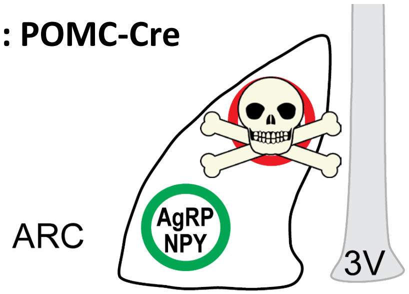


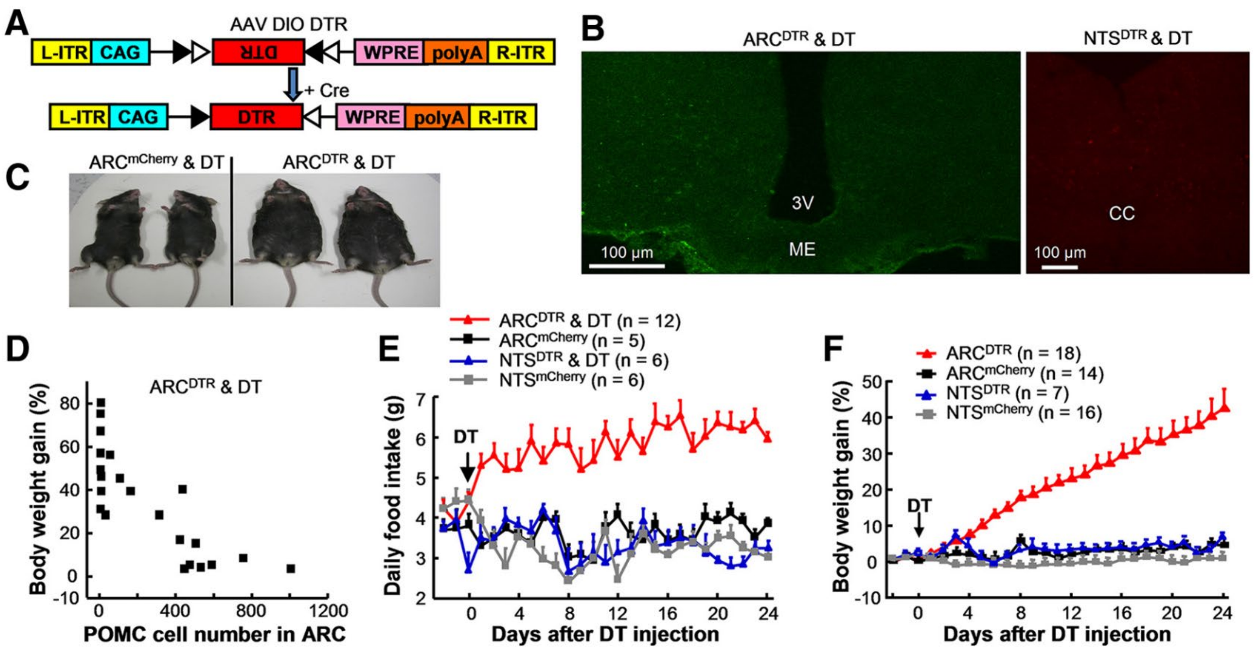
Aponte et al., *Nat Neurosci, 2011*

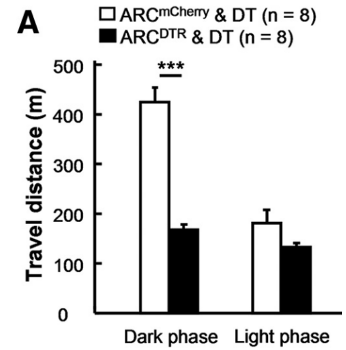
⇒ Chronic optogenetic stimulation of POMC neurons in ARC has anorexigenic effect

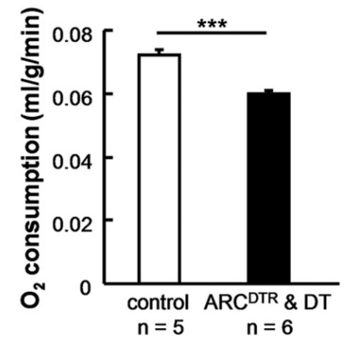
Testing the role of POMC neurons in ARC: genetic ablation experiment

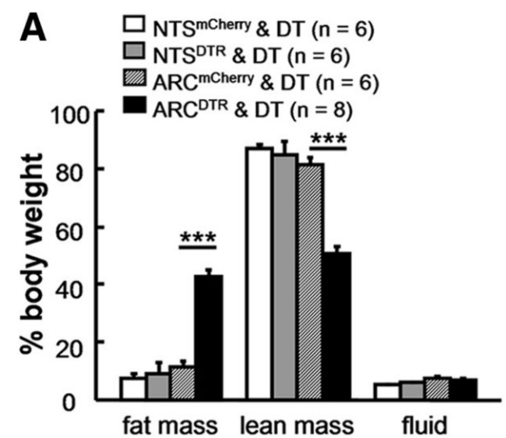
Mice: POMC-Cre











Zhan, Zhou et al., *J Neurosci, 2013*

⇒ In contrast, ablation of ARC POMC neurons in ARC activates anabolic (energy saving) mode

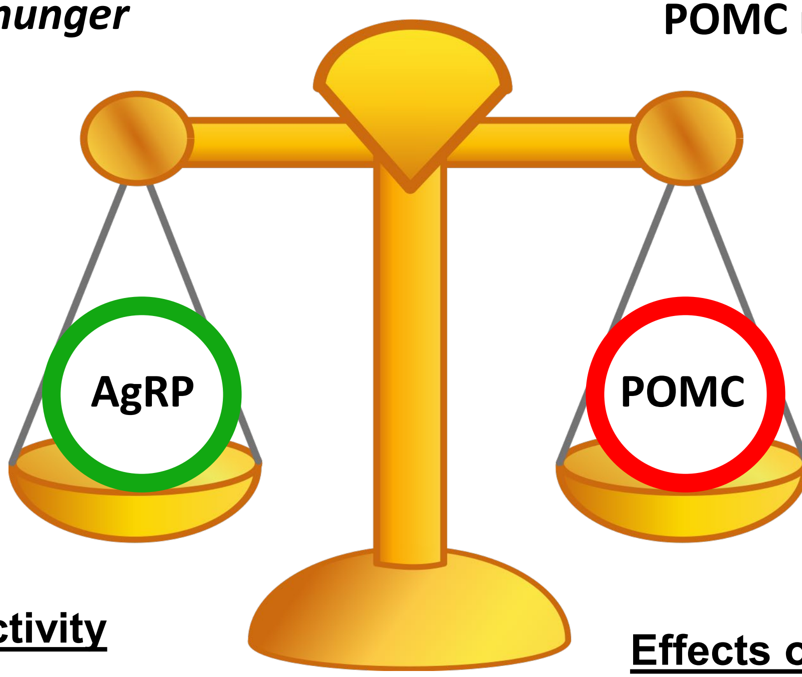
AgRP and POMC neurons: sensors of hunger and satiety states, respectively

AgRP respond *in vivo* to: *hunger*

- food restriction ↑
- Ghrelin ↑
- Leptin ↓
- food intake ↓
- …

POMC respond *in vivo* to: *satiety*

- glucose ↑
- Ghrelin ↓
- Leptin ↑
- …



<u>Effects of manipulating activity</u>

AgRP stimulation: *anabolic*

- voracious eating
- searching for food
- weight gain

AgRP inhibition: *catabolic*

- low appetite
- weight loss

AgRP loss: *anorexia, death*

<u>Effects of manipulating activity</u>

POMC stimulation: *catabolic*

- lower appetite
- chronic weight loss

POMC inhibition/loss: *anabolic*

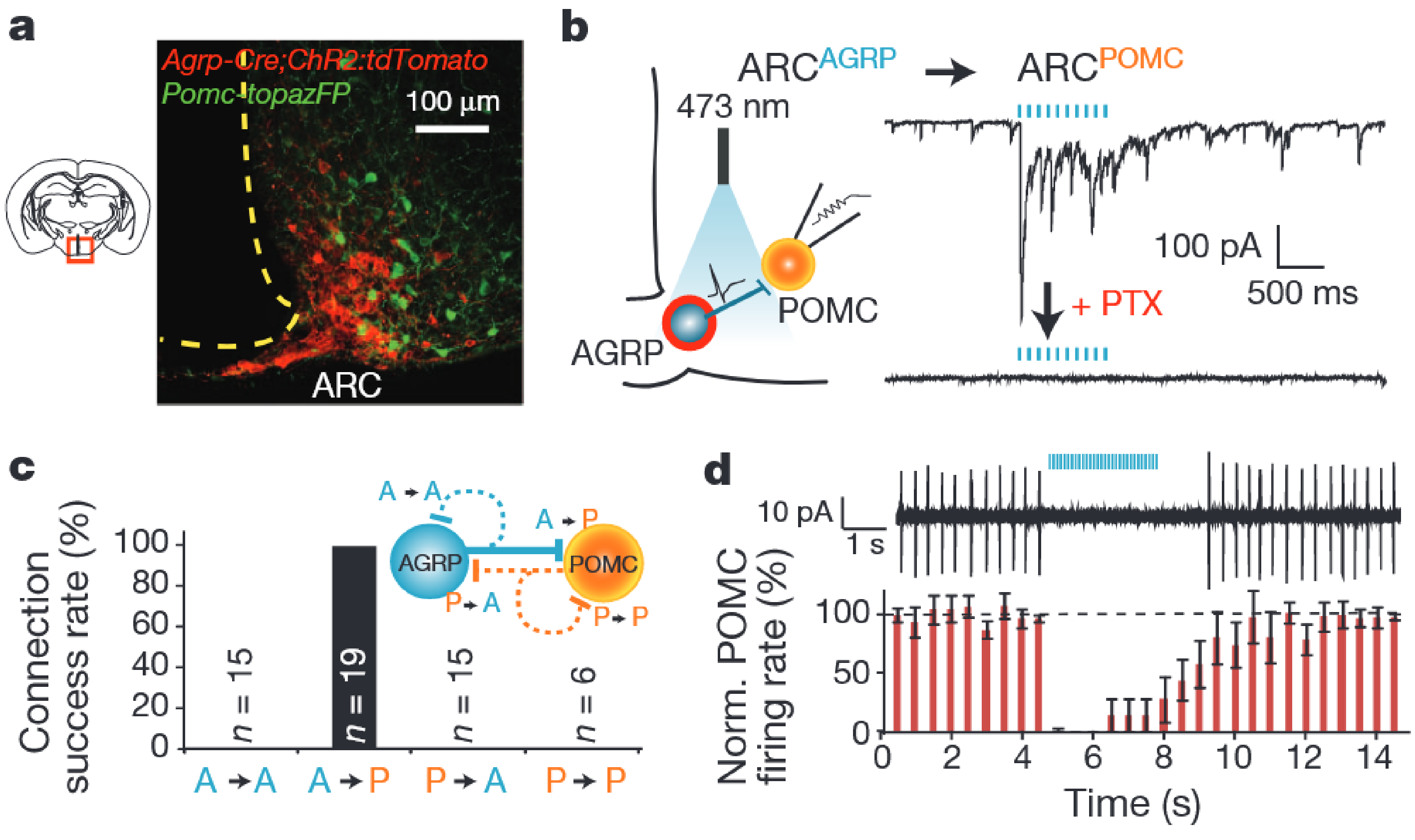
- increased food intake
- weight gain (fat)
- lower metabolism

II. Neural circuits of hunger and satiety

d) local- and long-range inhibition by the AgRP arcuate neurons

QUESTION: what is the network role of AgRP neurons in feeding control?

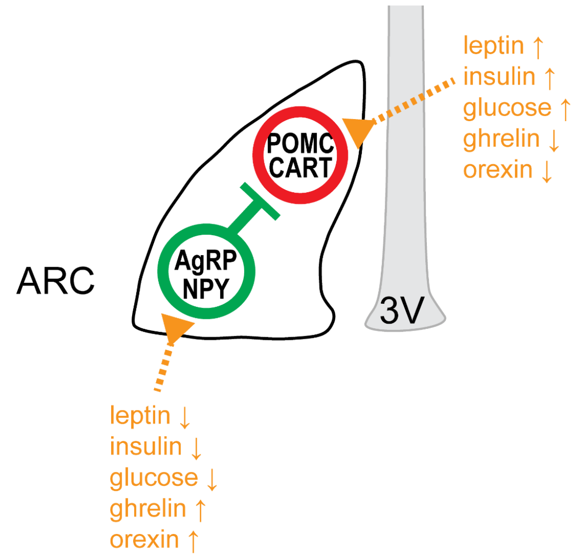
AgRP locally and unidirectionally inhibits POMC neurons in the ARC

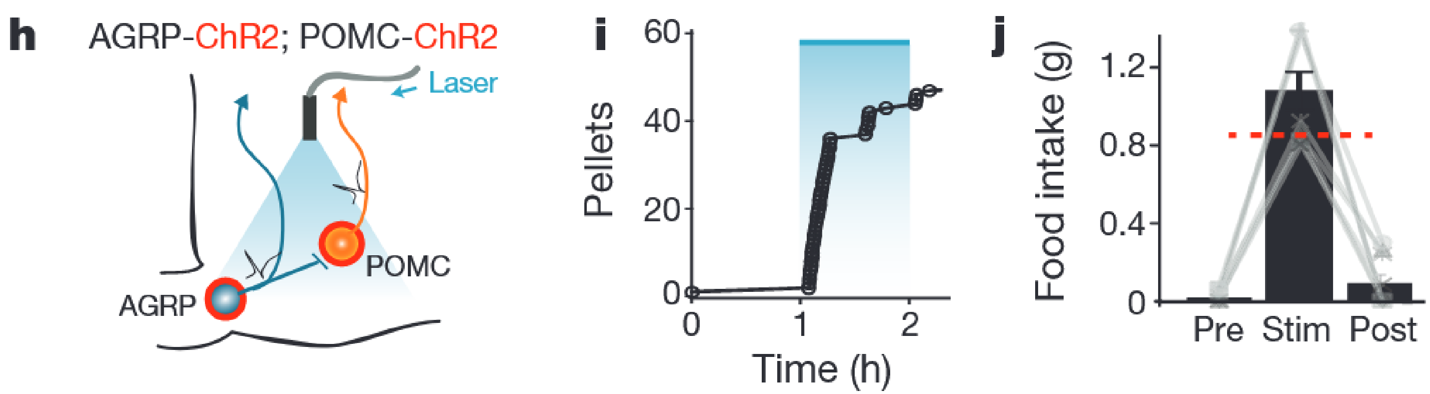


Atasoy et al., *Nature, 2012*

⇒ **Hunger-sensing GABAergic AgRP neurons locally suppress activity of satiety-sensing glutamatergic POMC neurons**

Co-activation of AgRP and POMC neurons in ARC: AgRP-mediated effect dominates

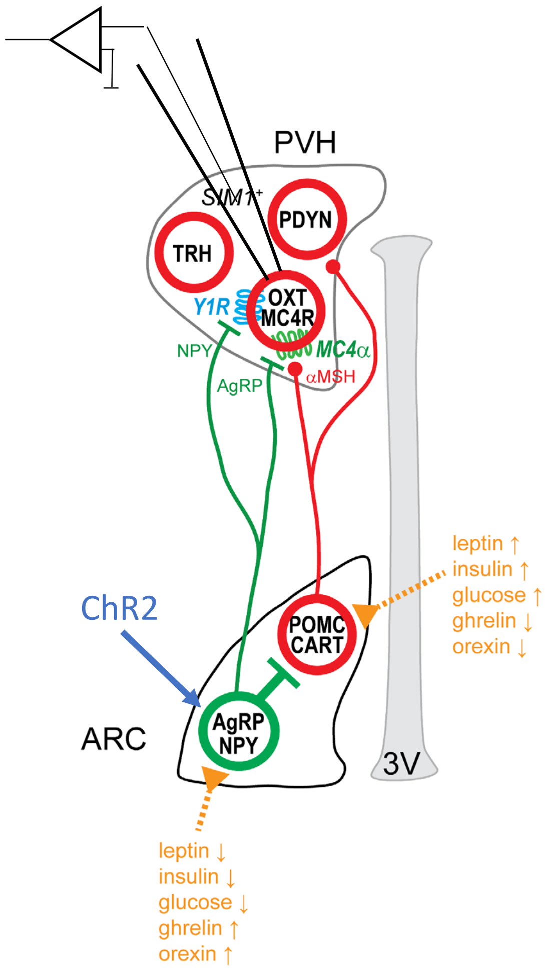




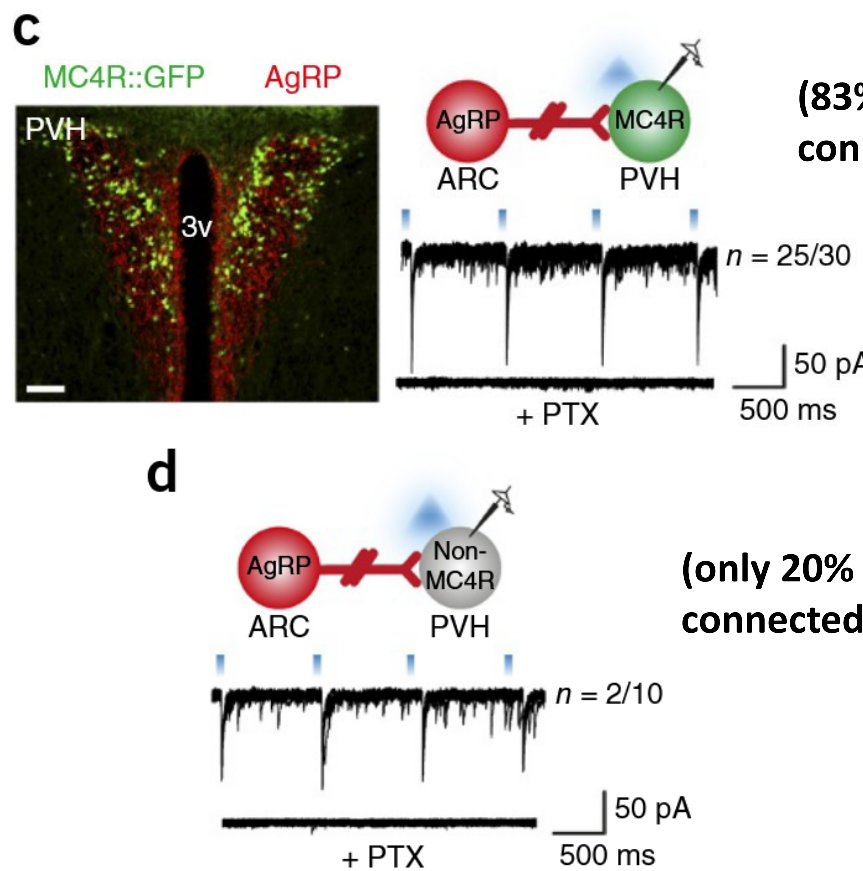
Atasoy et al., *Nature, 2012*

⇒ AgRP neurons most likely inhibit other tagrets outside the ARC nucleus

AgRP ARC neurons selectively target MC4 receptor expressing PVH neurons



Mice: MC4R-Cre x AgRP-Cre



(83% connected)

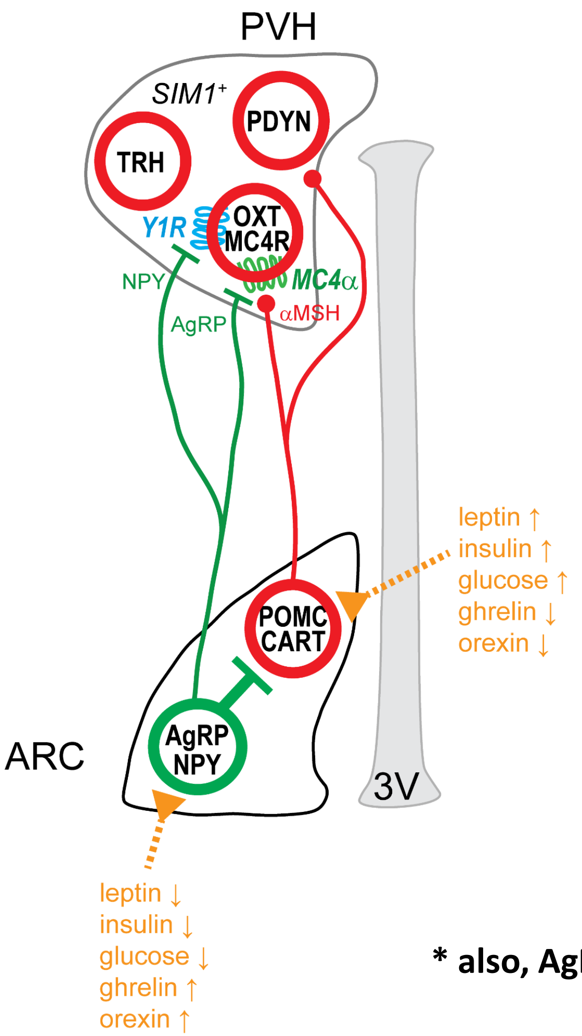
(only 20% connected)

Garfield et al., *Nat Neurosci, 2015*

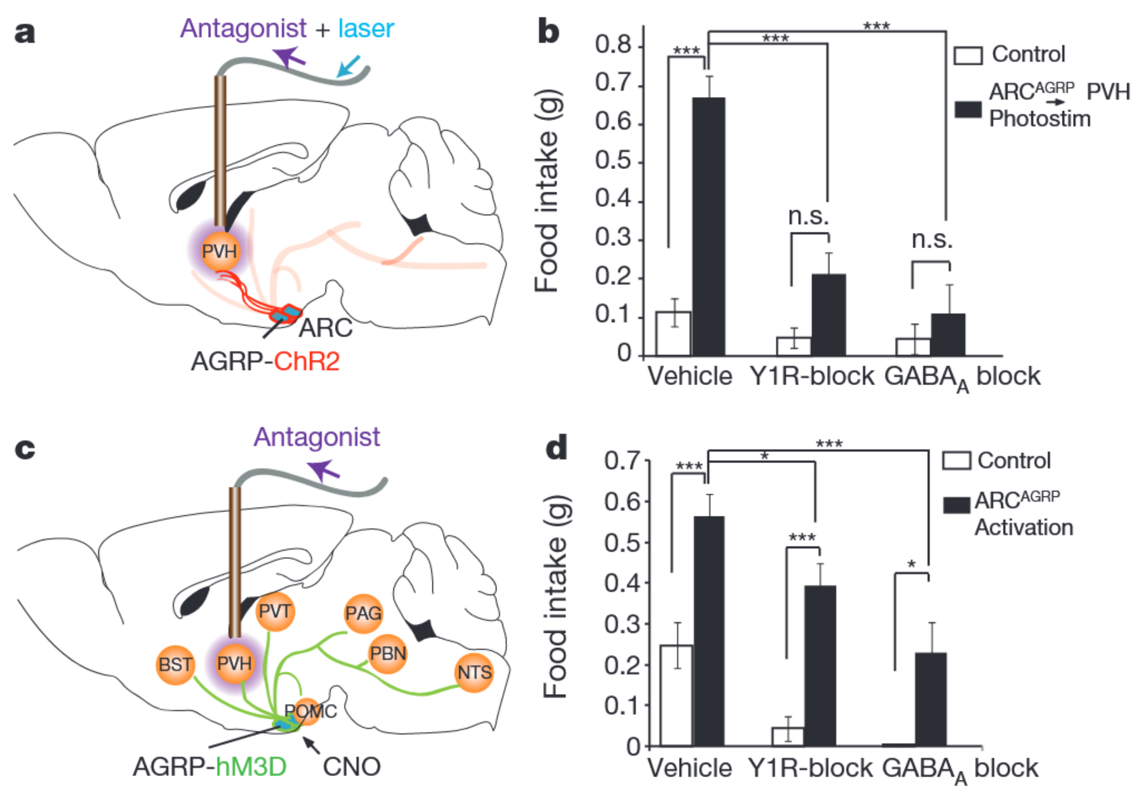
⇒ **AgRP neurons inhibit MC4R⁺ neurons in the PVH**

⇒ **This effect is likely due to GABA and peptidergic co-transmission**

AgRP ARC neurons selectively target MC4 receptor expressing PVH neurons



Mice: AgRP-Cre; ChR2 in ARC



Atasoy et al., *Nature, 2012*

*** also, AgRP is an antagonist of MC4 receptor**

⇒ NPY is co-released from AgRP/NPY neurons and contributes to PVH inhibition

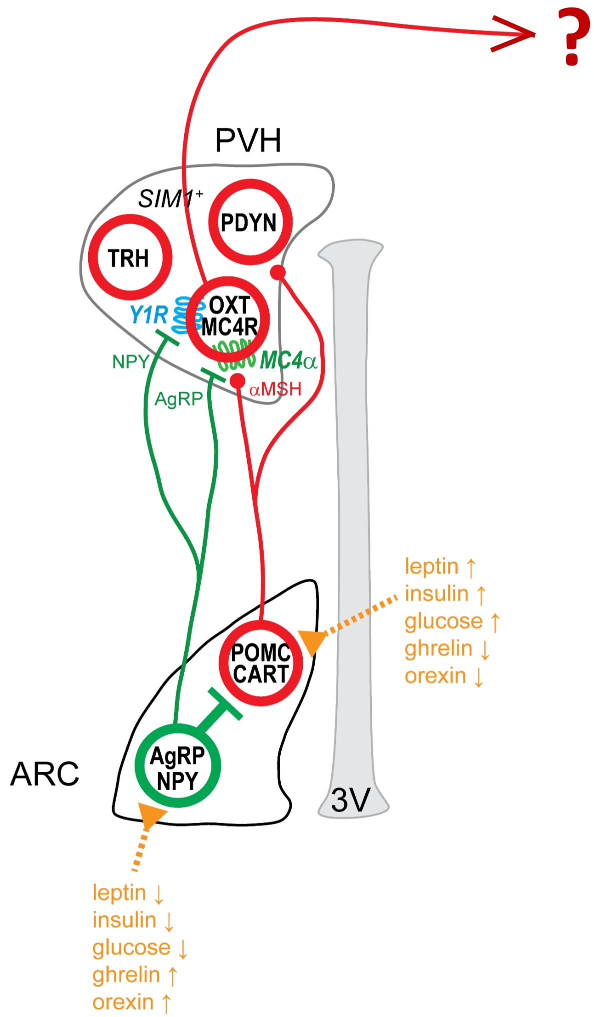
⇒ Effect of AgRP activity on feeding is partially confined to ARC->PVH circuit

II. Neural circuits of hunger and satiety

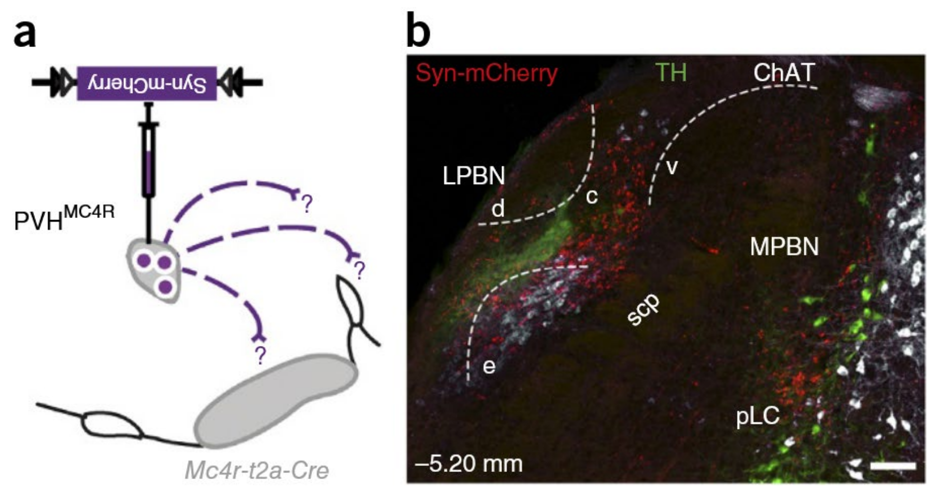
e) role of PVH in regulation of appetite

QUESTION: does PVH signal satiety and negatively control feeding?

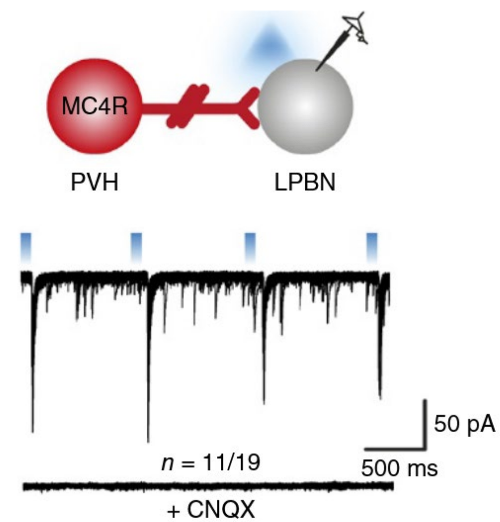
Possible downstream target: MC4R⁺ neurons synapse in the lateral parabrachial nucleus



Mice: MC4R-Cre; Synaptophysin-mCherry in PVN



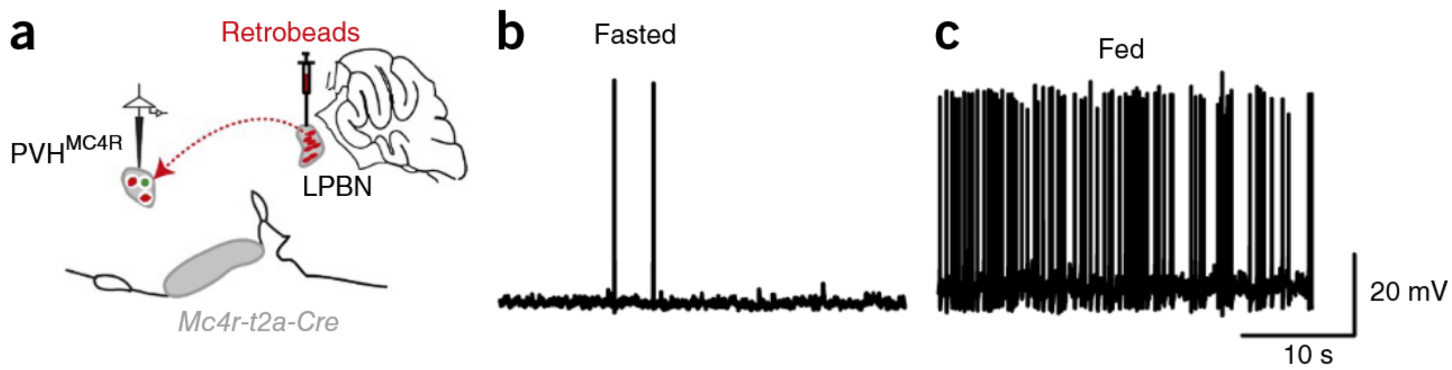
LPBN = lateral PBN (parabrachial nucleus)



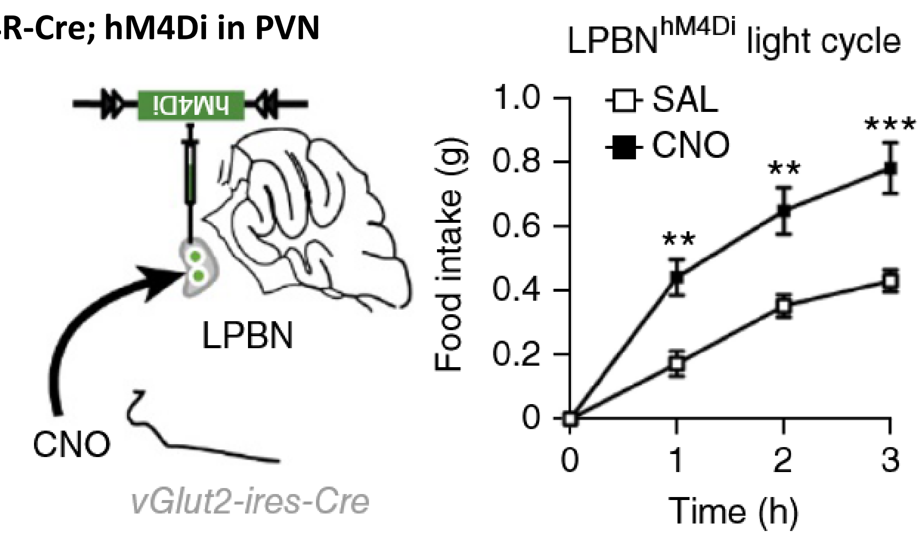
Garfield et al., *Nat Neurosci, 2015*

⇒ MC4R⁺ PVH neurons project to LPBN and excite glutamatergic neurons therein

PVH to LPBN circuit is active at satiety state and has anorexigenic effect



Mice: MC4R-Cre; hM4Di in PVN



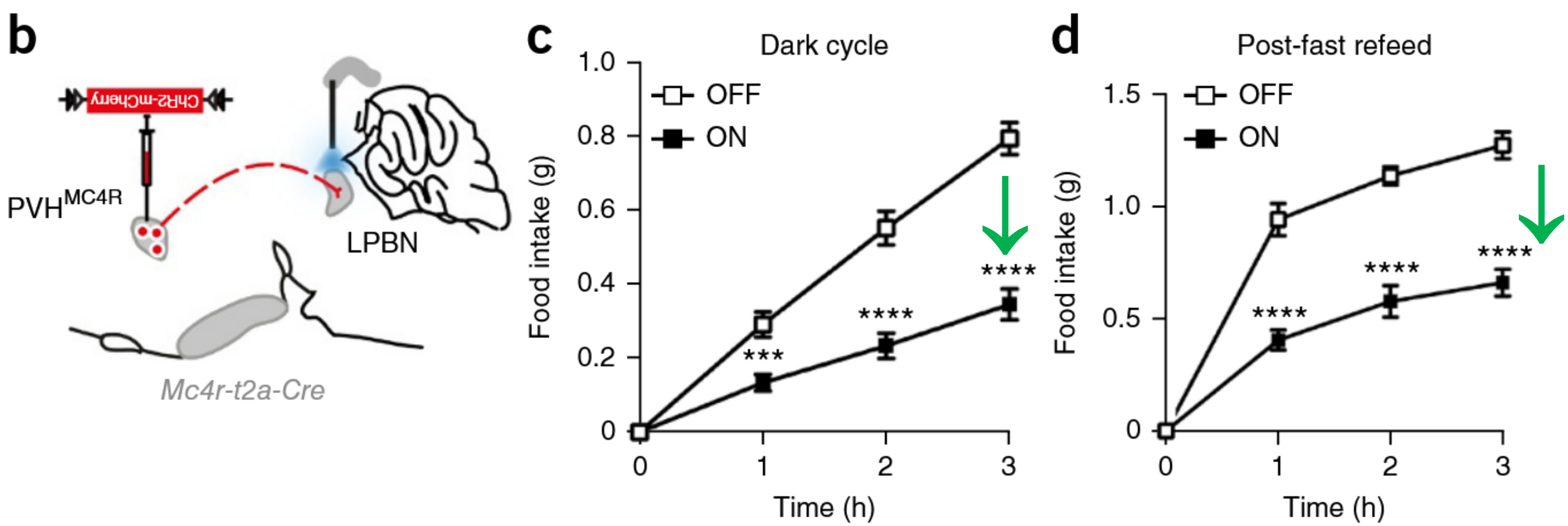
Garfield et al., *Nat Neurosci, 2015*

⇒ **LPBN-projecting PVH MCR4⁺ neurons fire more at satiety state**

⇒ **Chemogenetic inhibition of LPBN postsynaptic vGluT2⁺ neurons increases feeding**

PVH to LPBN circuit has anorexic effect

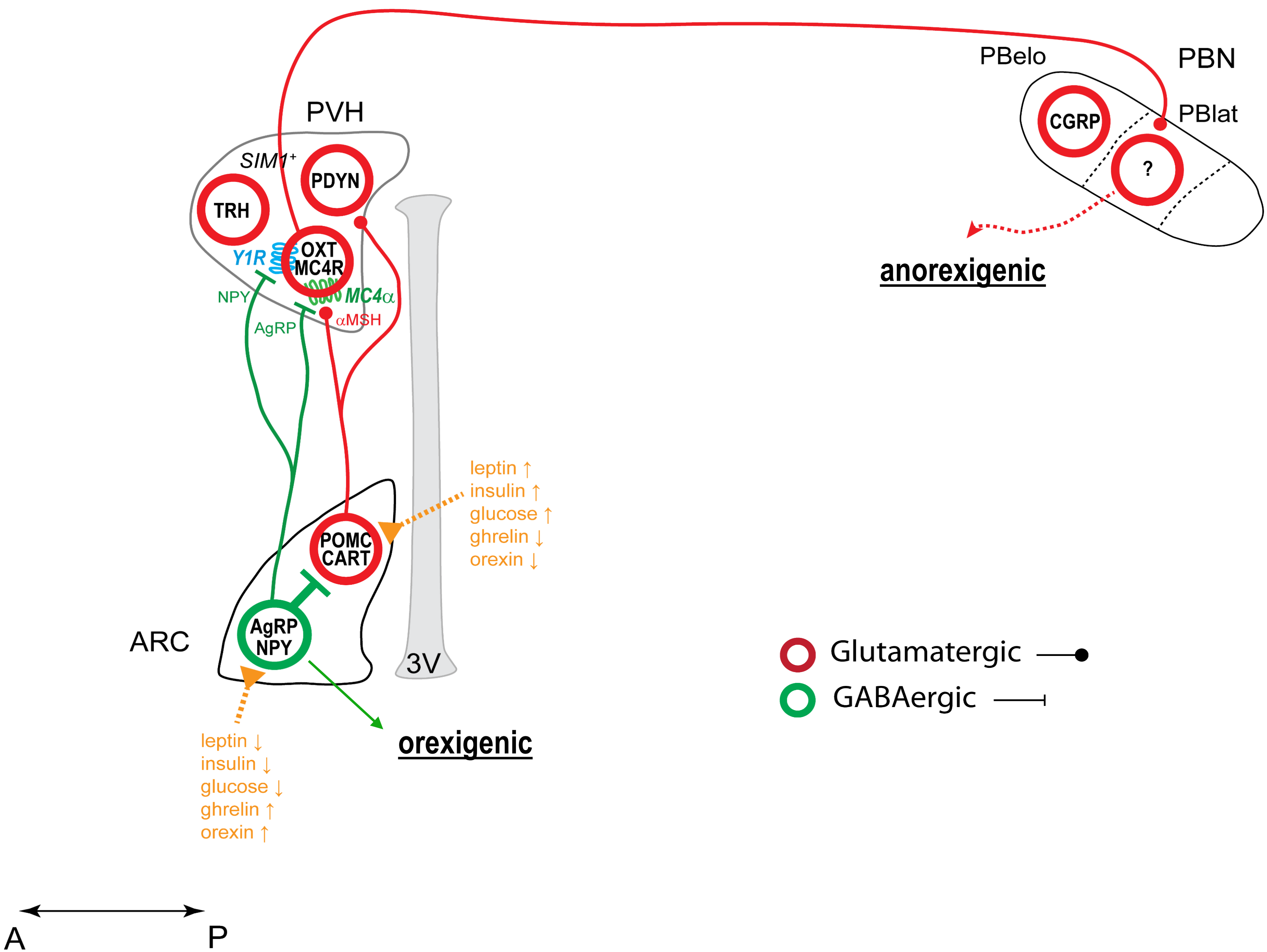
Mice: MC4R-Cre; ChR2 in PVN



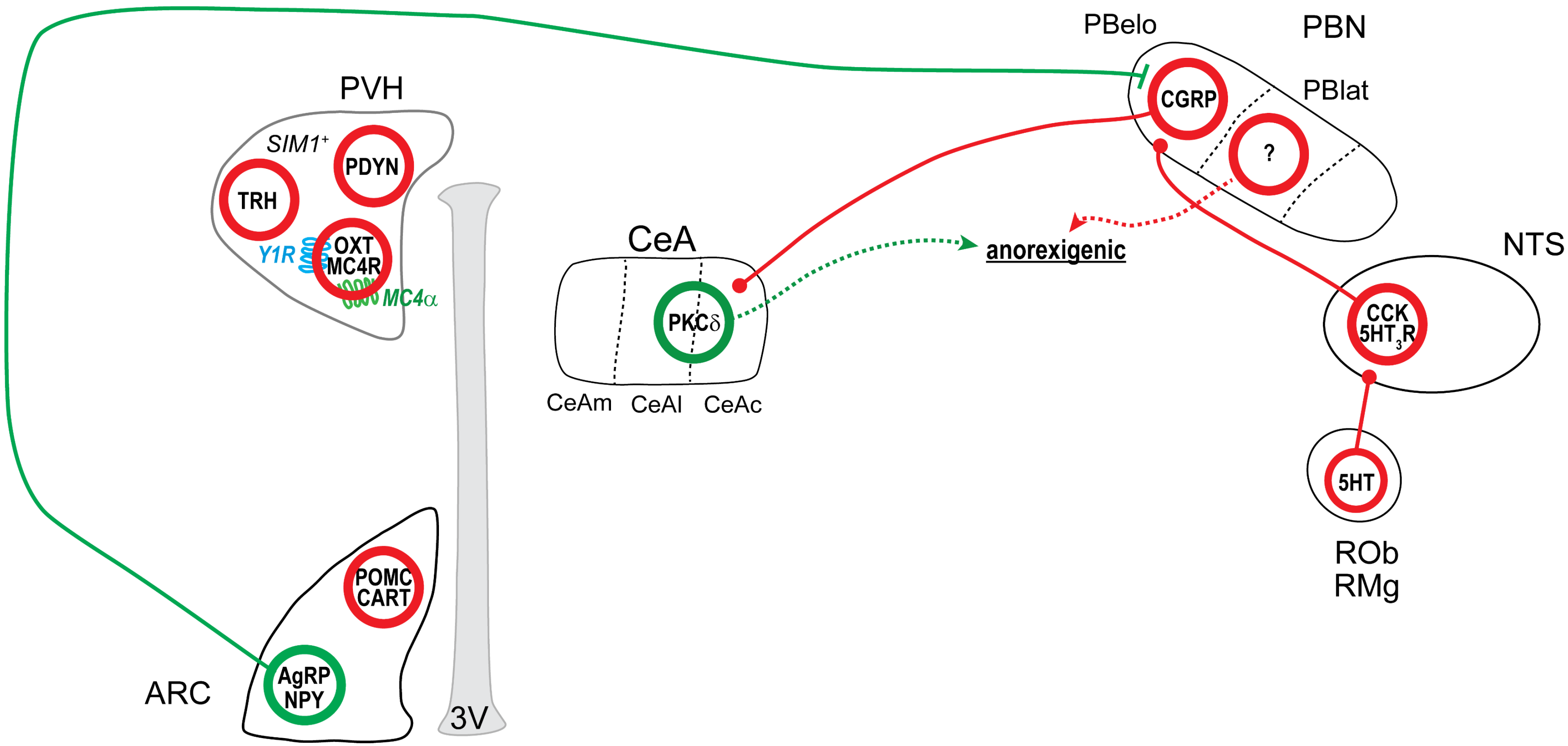
Garfield et al., *Nat Neurosci, 2015*

⇒ **Optogenetic stimulation of PVH MC4R⁺ terminals in LPBN reduces feeding even in fasted (very hungry) animals**

Summary: feeding control circuit from ARC to PBN via PVH



Exercise reading to explore the role of PBN->CeA circuit in feeding (malaise part of PBN)



LETTER

doi:10.1038/nature12596

Genetic identification of a neural circuit that suppresses appetite

Matthew E. Carter[1,2]†, Marta E. Soden[3,4], Larry S. Zweifel[3,4] & Richard D. Palmiter[1,2]

II. Neural circuits of hunger and satiety

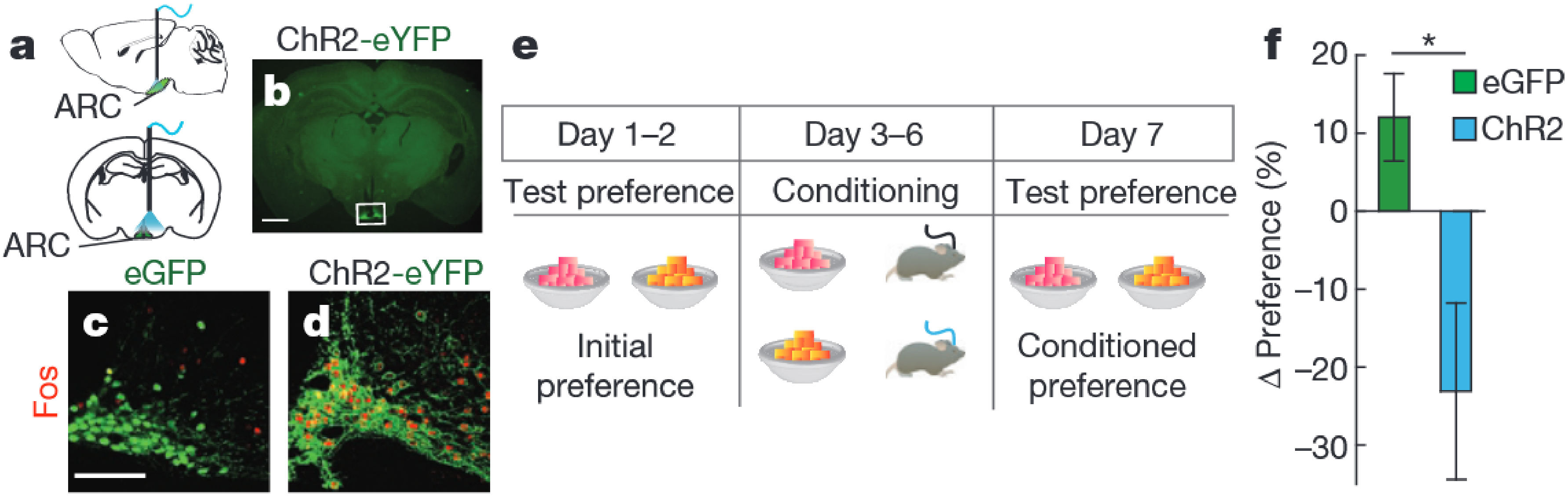
f) motivational valency of hunger and satiety imposed by the ARC-PVH circuit

QUESTION: is the activity of hunger- and satiety responsive neurons perceived as aversive or as rewarding?

AgRP neuronal activity influences preference for flavour (triggers aversion)

Mice: AgRP-Cre; ChR2 in ARC

Non-nutricious gels with different flavours

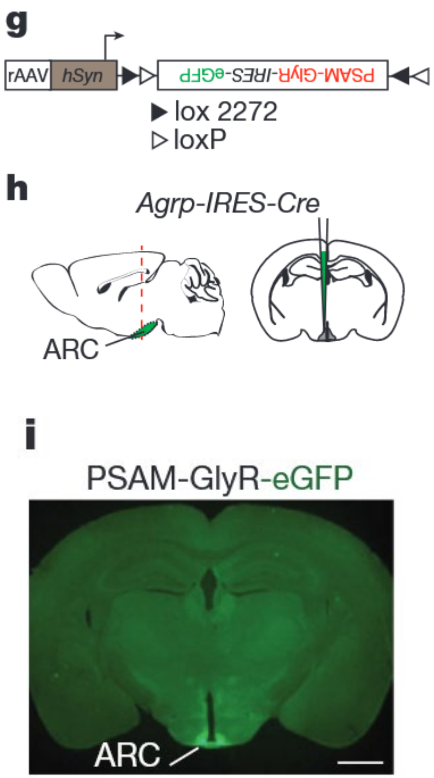


Betley et al., *Nature, 2015*

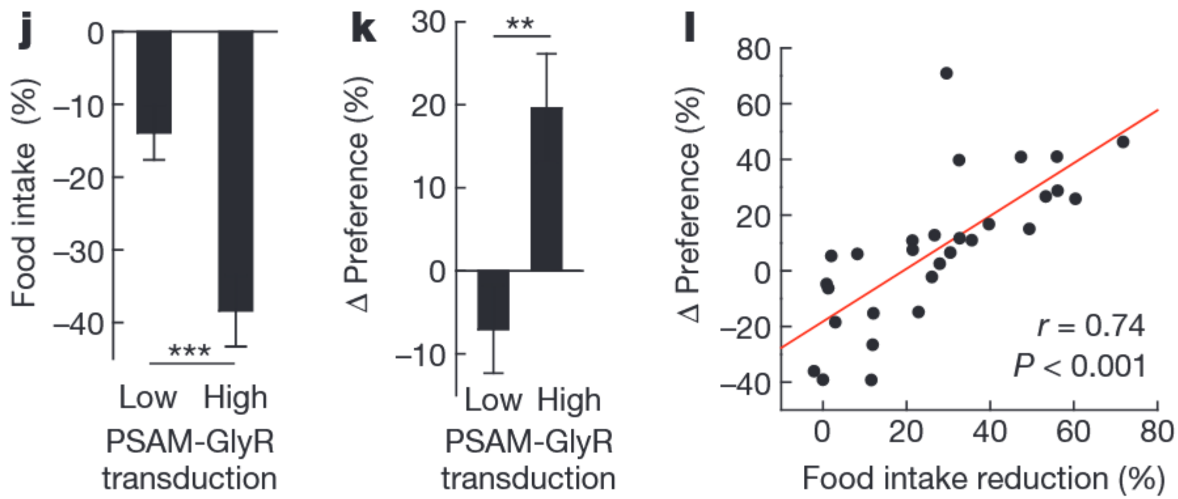
⇒ **Optogenetic stimulation of ARC AgRP neurons causes negative preference for flavour**

Suppression of AgRP activity causes preference for flavour

Mice: AgRP-Cre; Glycine receptor-based iDREADD into ARC



Flavour preference experiment (non-nutricious gels)

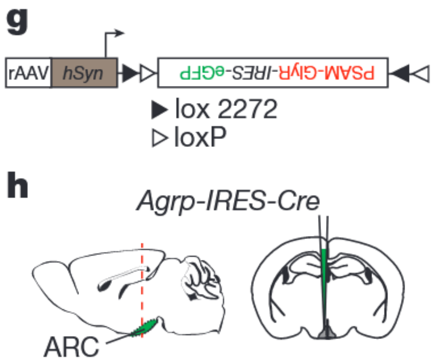


Betley et al., *Nature, 2015*

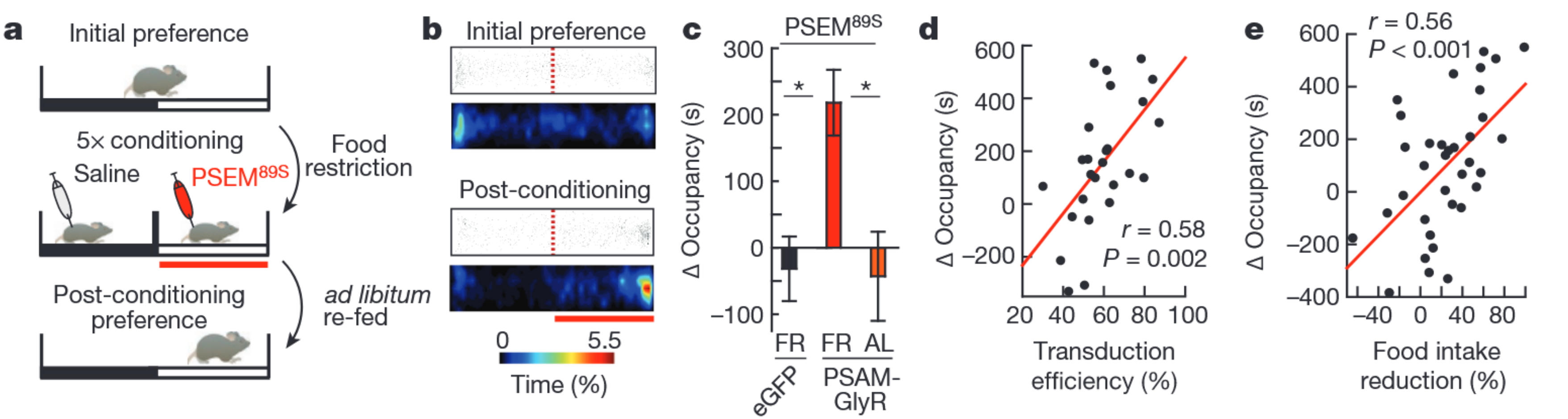
⇒ Chemogenetic inhibition of ARC AgRP neurons causes positive preference for flavour

Suppression of AgRP activity causes conditioned place preference in hungry mice

Mice: AgRP-Cre; Glycine receptor-based iDREADD into ARC



CPP / CPA test for AgRP neuron inhibition



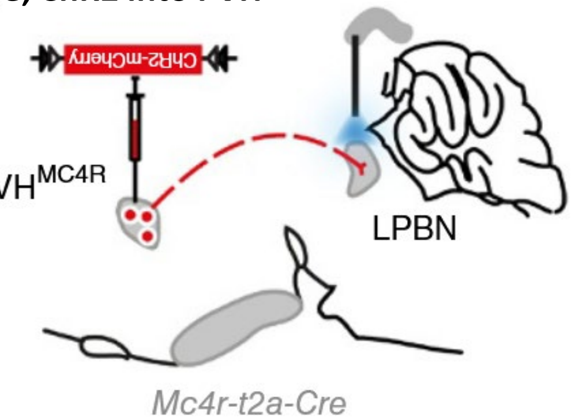
Betley et al., *Nature, 2015*

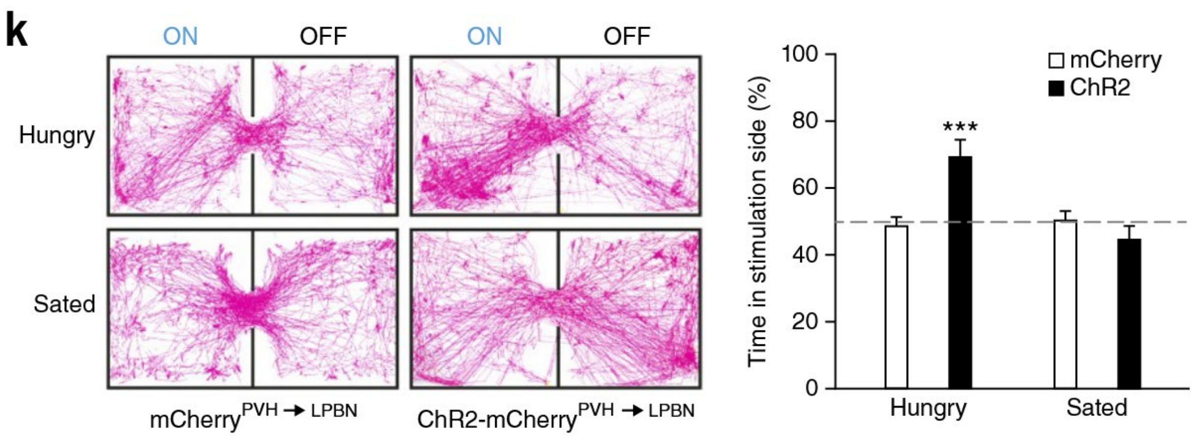
⇒ **Chemogenetic inhibition of ARC AgRP neurons causes positive preference for context if the animals were food-restricted (FR) during conditioning, not if *ad libitum* fed (AL)**

Activation of MC4R⁺ PVH neurons causes conditioned place preference in hungry mice

Mice: MC4R-Cre; ChR2 into PVH

Real-time place preference experiment



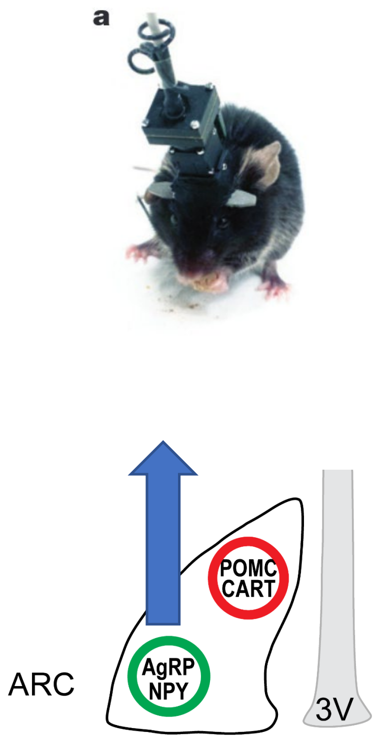


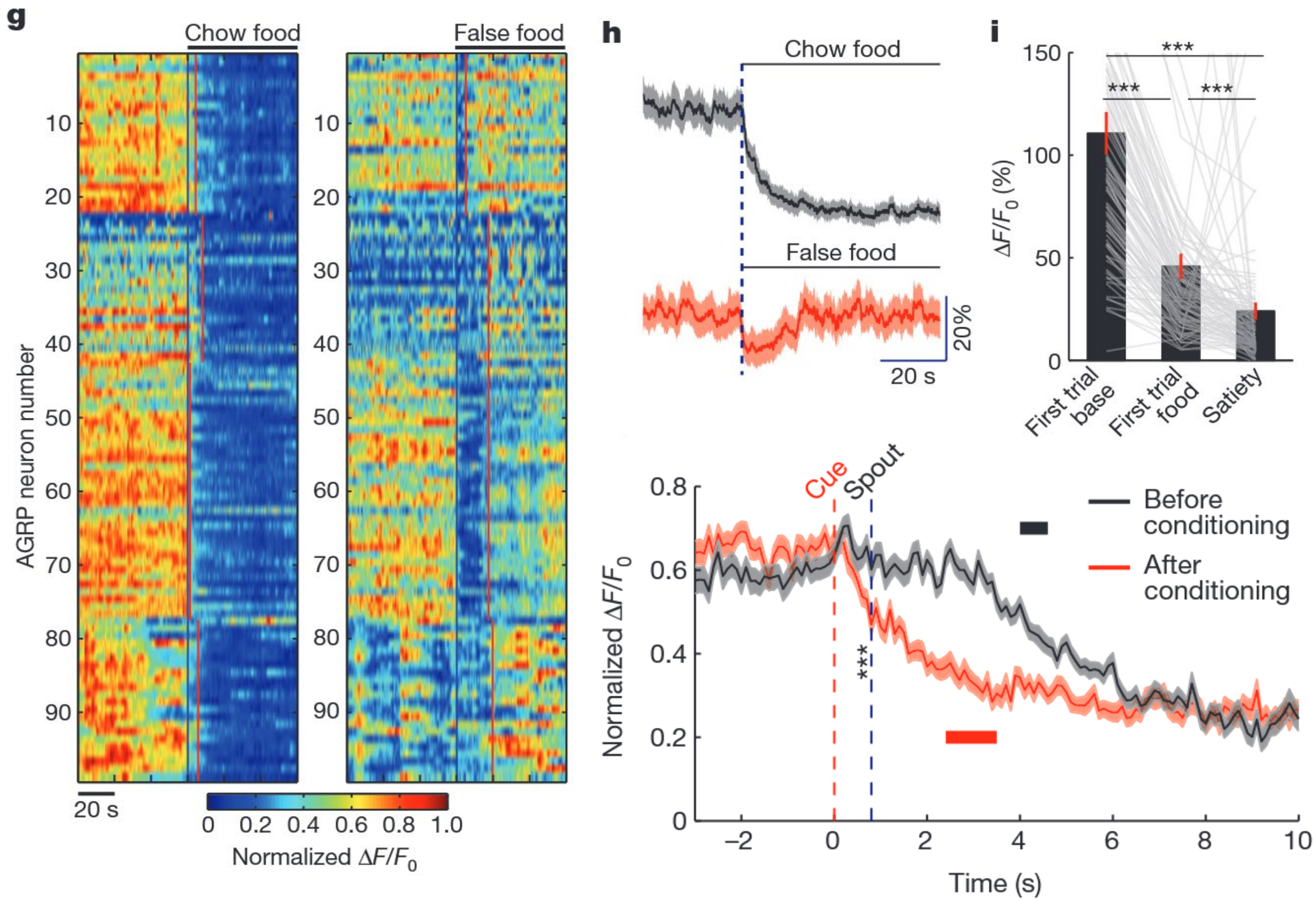
Garfield et al., *Nat Neurosci, 2015*

⇒ **Optogenetic stimulation of PVH MC4R⁺ neurons causes positive preference for context if the animals were food-restricted**

AgRP neuron activity is predictive, based of food quality, taste, memory, etc.

Mice: AgRP-ires-Cre, injected GCaMP6 into ARC



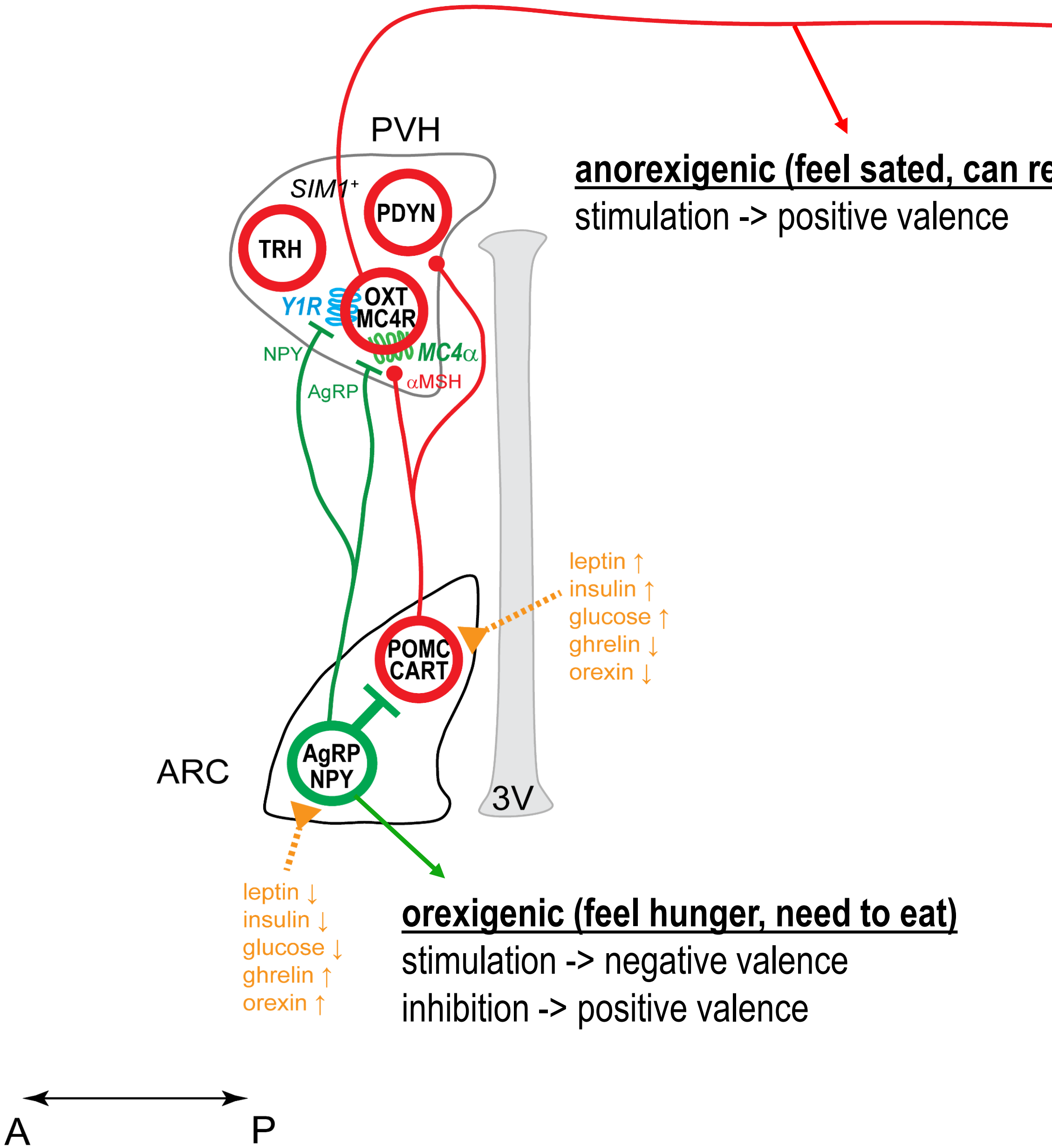


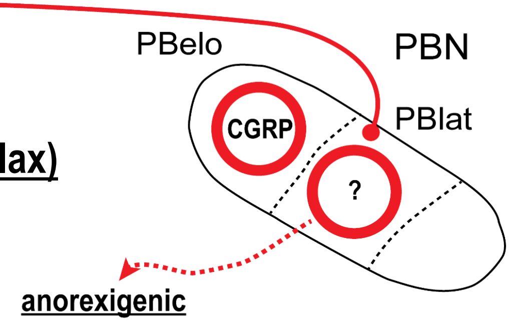
Remember similar anticipatory phenomena observed in thirst (Week 7)!

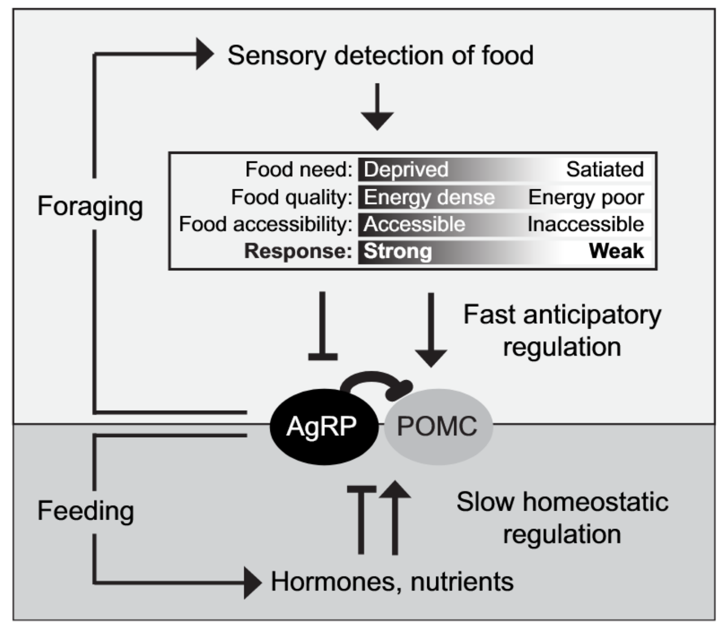
Betley et al., *Nature, 2015*

- ⇒ **In food-restricted mice, AgRP neurons react immediately on food presentation**
- ⇒ **Activity of AgRP neurons is reset if the food is removed or turns out false**
- ⇒ **Decrease of firing frequency predicts food-associated cue after conditioning**

Summary: AgRP-POMC-PVH neurons reflect motivational values of hunger and satiety

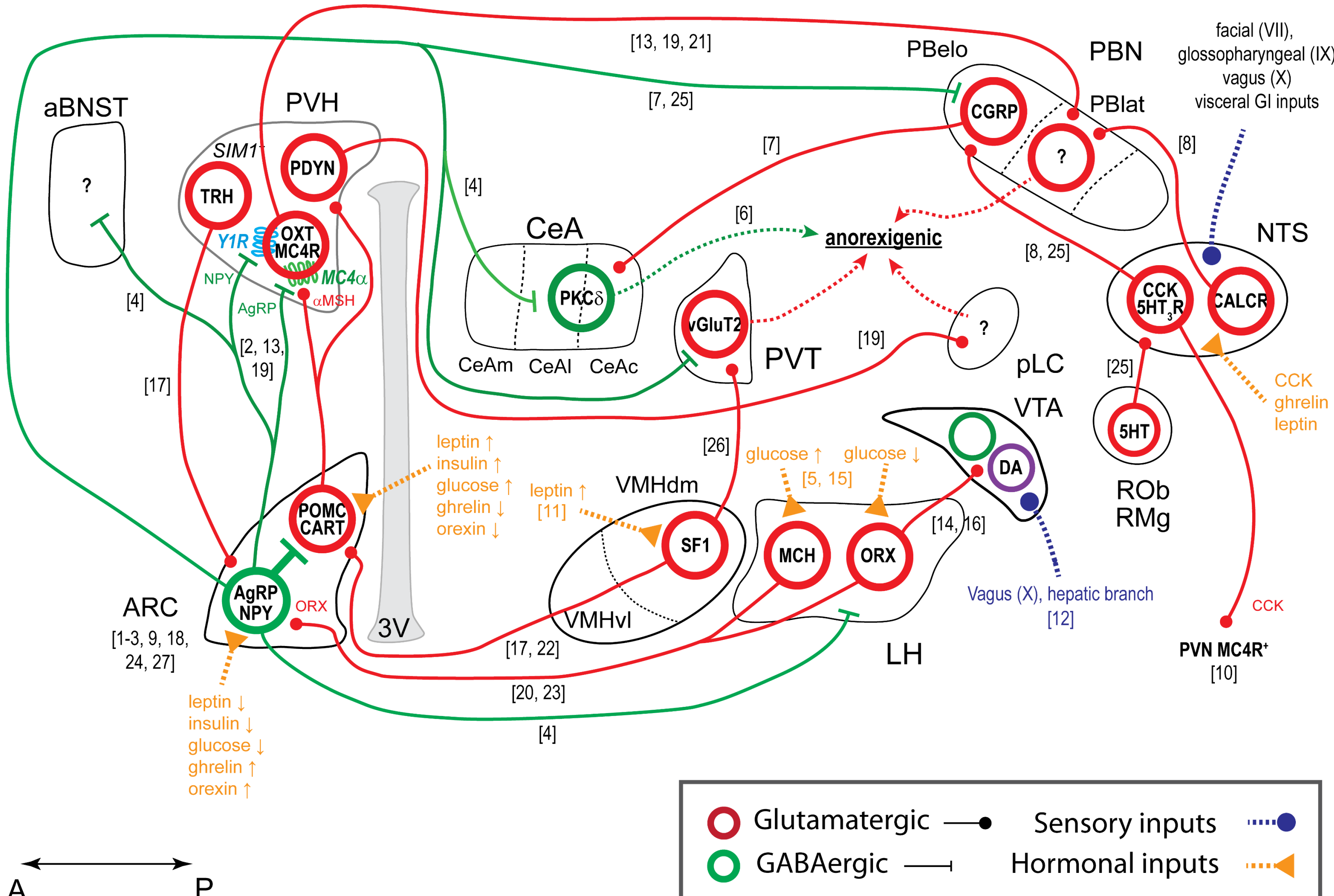






Chen et al., *Cell, 2015*

More detailed, but far from complete, schematic circuitry of feeding control (for geeks)



Molecular keys:
αMSH: melanocyte stimulating hormone
CART: cocaine-amphetamine-related transcript
POMC: proopiomelanocortin
NPY: neuropeptide Y
AgRP: agouti-related protein
MC4R: MC4 receptor for αMSH
Y1r: NPY receptor 1
CCK: cholecystokinin
SF1: steroidogenic factor 1

Anatomical keys:
aBNST: anterior bed nucleus of stria terminalis
ARC: arcuate hypothalamic nucleus
PVH: paraventricular hypothalamic nucleus
3V: 3rd ventricle
CeA: central amygdala (medial, lateral, capsular)
NTS: nucleus of tractus solitarius
PVT: paraventricular thalamus
VMH: ventromedial hypothalamic nucleus
LH: lateral hypothalamic area
VTA: ventral tegmental area
pLC: locus ceruleus posterior
ROb, RMg: raphe obscurus and magnus
PBN: parabrachial nucleus
PBelo: parabrachial outer external lateral

References for the schematic

1. Aponte, Y., Atasoy, D., and Sternson, S.M. (2011). AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci *14*, 351–355. 10.1038/nn.2739.
2. Atasoy, D., Betley, J.N., Su, H.H., and Sternson, S.M. (2012). Deconstruction of a neural circuit for hunger. Nature *488*, 172–177. 10.1038/nature11270.
3. Betley, J.N., Xu, S., Cao, Z.F.H., Gong, R., Magnus, C.J., Yu, Y., and Sternson, S.M. (2015). Neurons for hunger and thirst transmit a negative-valence teaching signal. Nature *521*, 180–185. 10.1038/nature14416.
4. Betley, J.N., Cao, Z.F.H., Ritola, K.D., and Sternson, S.M. (2013). Parallel, redundant circuit organization for homeostatic control of feeding behavior. Cell *155*, 1337–1350. 10.1016/j.cell.2013.11.002.
5. Burdakov, D., Gerasimenko, O., and Verkhratsky, A. (2005). Physiological changes in glucose differentially modulate the excitability of hypothalamic melanin-concentrating hormone and orexin neurons in situ. J Neurosci *25*, 2429–2433. 10.1523/JNEUROSCI.4925-04.2005.
6. Cai, H., Haubensak, W., Anthony, T.E., and Anderson, D.J. (2014). Central amygdala PKC-δ(+) neurons mediate the influence of multiple anorexigenic signals. Nat Neurosci *17*, 1240–1248. 10.1038/nn.3767.
7. Carter, M.E., Soden, M.E., Zweifel, L.S., and Palmiter, R.D. (2013). Genetic identification of a neural circuit that suppresses appetite. Nature *503*, 111–114. 10.1038/nature12596.
8. Cheng, W., Gonzalez, I., Pan, W., Tsang, A.H., Adams, J., Ndoka, E., Gordian, D., Khoury, B., Roelofs, K., Evers, S.S., et al. (2020). Calcitonin Receptor Neurons in the Mouse Nucleus Tractus Solitarius Control Energy Balance via the Non-aversive Suppression of Feeding. Cell Metab *31*, 301-312.e5. 10.1016/j.cmet.2019.12.012.
9. Cowley, M.A., Smith, R.G., Diano, S., Tschöp, M., Pronchuk, N., Grove, K.L., Strasburger, C.J., Bidlingmaier, M., Esterman, M., Heiman, M.L., et al. (2003). The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron *37*, 649–661. 10.1016/s0896-6273(03)00063-1.
10. D'Agostino, G., Lyons, D.J., Cristiano, C., Burke, L.K., Madara, J.C., Campbell, J.N., Garcia, A.P., Land, B.B., Lowell, B.B., Dileone, R.J., et al. (2016). Appetite controlled by a cholecystokinin nucleus of the solitary tract to hypothalamus neurocircuit. eLife *5*, e12225. 10.7554/eLife.12225.
11. Dhillon, H., Zigman, J.M., Ye, C., Lee, C.E., McGovern, R.A., Tang, V., Kenny, C.D., Christiansen, L.M., White, R.D., Edelstein, E.A., et al. (2006). Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. Neuron *49*, 191–203. 10.1016/j.neuron.2005.12.021.
12. Fernandes, A.B., Alves Da Silva, J., Almeida, J., Cui, G., Gerfen, C.R., Costa, R.M., and Oliveira-Maia, A.J. (2020). Postingestive Modulation of Food Seeking Depends on Vagus-Mediated Dopamine Neuron Activity. Neuron *106*, 778-788.e6. 10.1016/j.neuron.2020.03.009.
13. Garfield, A.S., Li, C., Madara, J.C., Shah, B.P., Webber, E., Steger, J.S., Campbell, J.N., Gavrilova, O., Lee, C.E., Olson, D.P., et al. (2015). A neural basis for melanocortin-4 receptor-regulated appetite. Nat Neurosci *18*, 863–871. 10.1038/nn.4011.
14. Harris, G.C., Wimmer, M., and Aston-Jones, G. (2005). A role for lateral hypothalamic orexin neurons in reward seeking. Nature *437*, 556–559. 10.1038/nature04071.
15. Kong, D., Vong, L., Parton, L.E., Ye, C., Tong, Q., Hu, X., Choi, B., Brüning, J.C., and Lowell, B.B. (2010). Glucose Stimulation of Hypothalamic MCH Neurons Involves KATP Channels, Is Modulated by UCP2, and Regulates Peripheral Glucose Homeostasis. Cell Metabolism *12*, 545–552. 10.1016/j.cmet.2010.09.013.
16. Korotkova, T.M., Sergeeva, O.A., Eriksson, K.S., Haas, H.L., and Brown, R.E. (2003). Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. J Neurosci *23*, 7–11. 10.1523/JNEUROSCI.23-01-00007.2003.
17. Krashes, M.J., Shah, B.P., Madara, J.C., Olson, D.P., Strochlic, D.E., Garfield, A.S., Vong, L., Pei, H., Watabe-Uchida, M., Uchida, N., et al. (2014). An excitatory paraventricular nucleus to AgRP neuron circuit that drives hunger. Nature *507*, 238–242. 10.1038/nature12956.
18. Krashes, M.J., Koda, S., Ye, C., Rogan, S.C., Adams, A.C., Cusher, D.S., Maratos-Flier, E., Roth, B.L., and Lowell, B.B. (2011). Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. J Clin Invest *121*, 1424–1428. 10.1172/JCI46229.
19. Li, M.M., Madara, J.C., Steger, J.S., Krashes, M.J., Balthasar, N., Campbell, J.N., Resch, J.M., Conley, N.J., Garfield, A.S., and Lowell, B.B. (2019). The Paraventricular Hypothalamus Regulates Satiety and Prevents Obesity via Two Genetically Distinct Circuits. Neuron *102*, 653-667.e6. 10.1016/j.neuron.2019.02.028.
20. Ma, X., Zubcevic, L., Brüning, J.C., Ashcroft, F.M., and Burdakov, D. (2007). Electrical inhibition of identified anorexigenic POMC neurons by orexin/hypocretin. J Neurosci *27*, 1529–1533. 10.1523/JNEUROSCI.3583-06.2007.
21. Shah, B.P., Vong, L., Olson, D.P., Koda, S., Krashes, M.J., Ye, C., Yang, Z., Fuller, P.M., Elmquist, J.K., and Lowell, B.B. (2014). MC4R-expressing glutamatergic neurons in the paraventricular hypothalamus regulate feeding and are synaptically connected to the parabrachial nucleus. Proc. Natl. Acad. Sci. U.S.A. *111*, 13193–13198. 10.1073/pnas.1407843111.
22. Sternson, S.M., Shepherd, G.M.G., and Friedman, J.M. (2005). Topographic mapping of VMH --> arcuate nucleus microcircuits and their reorganization by fasting. Nat Neurosci *8*, 1356–1363. 10.1038/nn1550.
23. van den Top, M., Lee, K., Whyment, A.D., Blanks, A.M., and Spanswick, D. (2004). Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. Nat Neurosci *7*, 493–494. 10.1038/nn1226.
24. Vong, L., Ye, C., Yang, Z., Choi, B., Chua, S., Jr., and Lowell, B.B. (2011). Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. Neuron *71*, 142–154. 10.1016/j.neuron.2011.05.028.
25. Wu, Q., Clark, M.S., and Palmiter, R.D. (2012). Deciphering a neuronal circuit that mediates appetite. Nature *483*, 594–597. 10.1038/nature10899.
26. Zhang, J., Chen, D., Sweeney, P., and Yang, Y. (2020). An excitatory ventromedial hypothalamus to paraventricular thalamus circuit that suppresses food intake. Nat Commun *11*, 6326. 10.1038/s41467-020-20093-4.
27. Zhan, C., Zhou, J., Feng, Q., Zhang, J.-E., Lin, S., Bao, J., Wu, P., and Luo, M. (2013). Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. J Neurosci *33*, 3624–3632. 10.1523/JNEUROSCI.2742-12.2013.