Uneven balance power between hypothalamic peptidergic neurons in the control of feeding

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Background

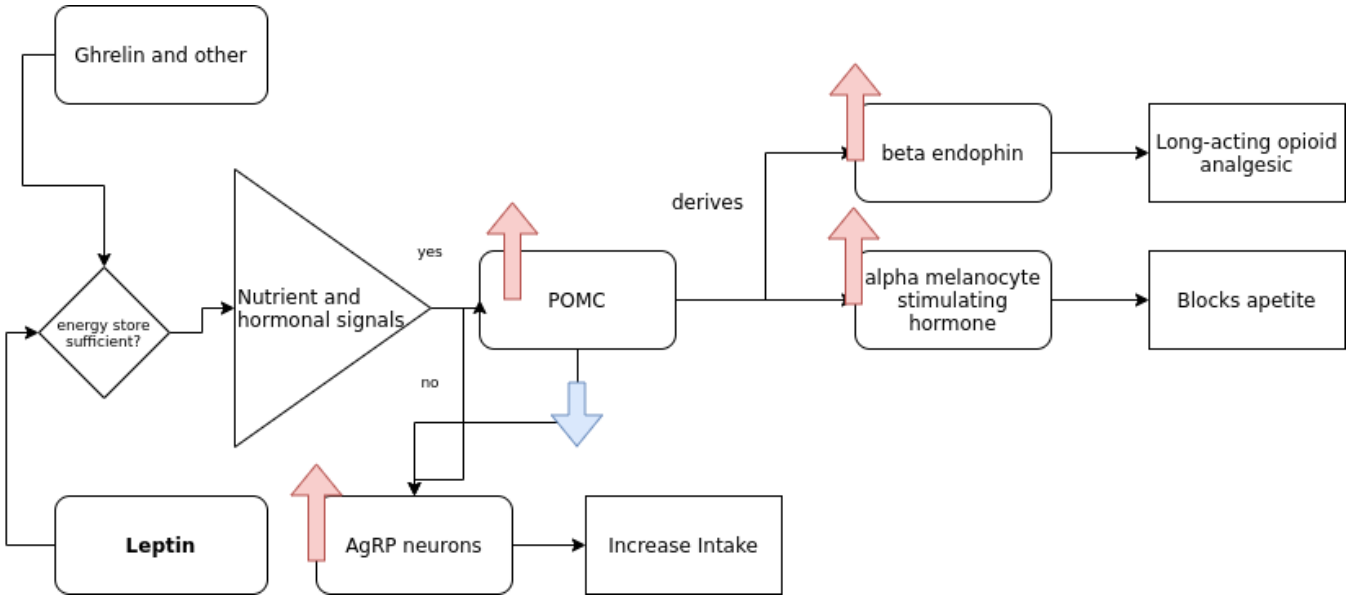
‘Hypothalamus plays an essential role in the regulation of feeding behavior’

- Ventromedial hypothalamus -> 'satiety center'
- Lateral hypothalamus -> 'feeding center'

Author's focus on the arcuate nucleus

- Agouticortin related protein (AgRP) -> orexigenic
- POMC -> anorexigenic

Proposed mechanism



Models

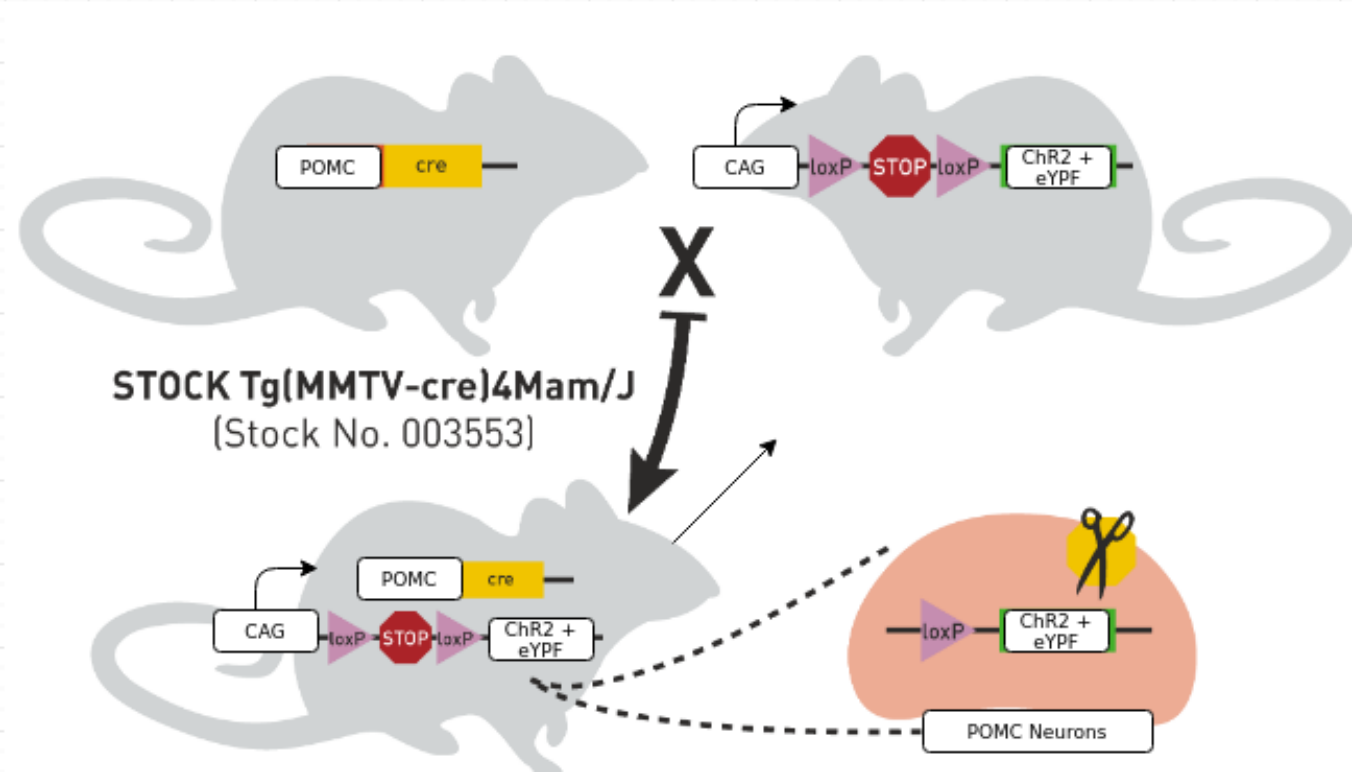
To test the previous mechanism experimental manipulation of both neuronal system is required

- POMC and NPY neurons share a common cellular origin
  - If origin is shared, then traditional transgenic mani
  - Virally mediated instead allows for selective POMC ne

Model 1: viral POMC-ChR2

- Adeno-associated virus carries blue-light activation + fluorescent protein
- Not expressed because of inversion
- POMC-CRE inverts -> expression only in POMC

Model 2: embryonic POMC-expressing progrenitor control (sub-set AgRP/NPY + POMC)



- Ended up in AgRP/NPY blue light activated, green fluorescent protein model
- neuron depolarization -> cFos

With the models at hand, they tested intake dependent on differential activation

- ‘Rapid inhibition of feeding behavior in fasted viral POMC-ChR2 mice’
- ‘Rapid and robust increase in food intake in Tg POMC-ChR2 mice’

Results

Experimental setup

- ad libitum access to standard laboratory pellet before and after tests
- testes at same time of the day
- when food deprived: 4 hours + ad libitum water

‘Rapid inhibition of feeding behavior in fasted viral POMC-ChR2 mice’

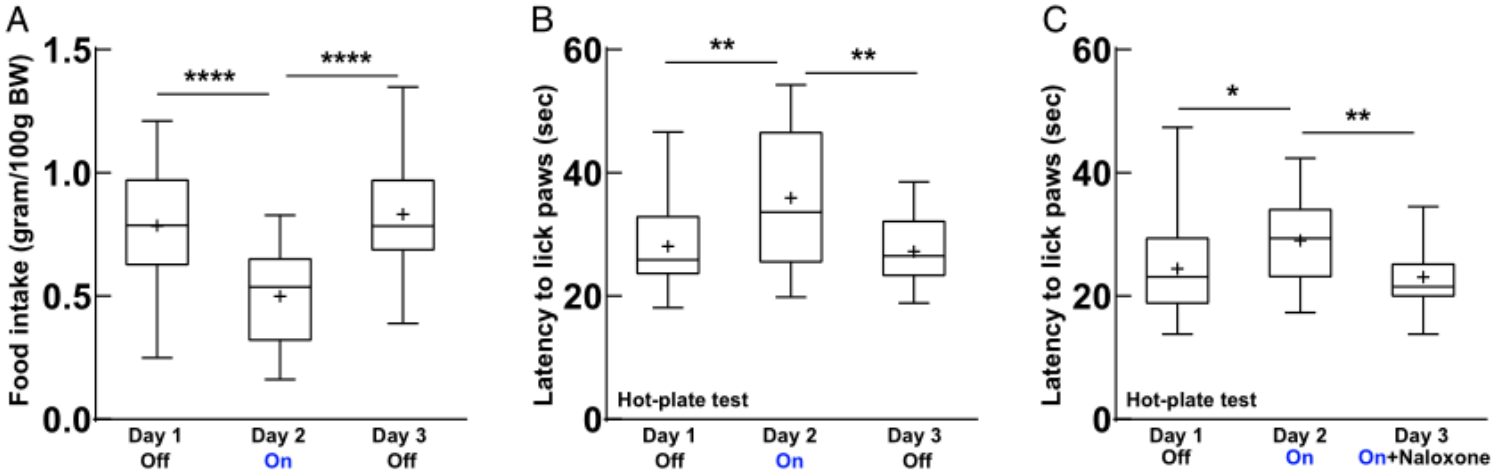


Fig. 3. Selective activation of POMC neurons in the Arc suppresses food intake in fasted viral POMC-ChR2 mice. (*A*) Blue light stimulation of POMC neurons induced a reduction of food intake in 4-h fasted viral POMC-ChR2 mice, $F(2, 40) = 18.99$, $P < 0.0001$; $^{****}P < 0.0001$; $n = 21$ mice. (*B*) Light stimulation of POMC neurons led to an increased latency for the mice to lick their paws during the hot-plate test, $F(2, 30) = 8.82$, $P < 0.01$; $^{**}P < 0.01$; $n = 16$ mice. (*C*) Increased latency induced by light stimulation was blunted by pretreatment with opioid antagonist naloxone (10 mg/kg) in the hot-plate test, $F(2, 28) = 6.797$, $P < 0.01$; $^{*}P < 0.05$; $^{**}P < 0.01$; $n = 15$ mice. Repeated-measures one-way ANOVA followed by Turkey’s test were used for all above statistics. Box plots show median, mean (+), lower and upper quartiles (boxes), and minima and maxima (whiskers).

- If activation of POMC-neurons is successful, then beta-endorphin + alpha-MSH should be active
- They previously showed that global POMC-neuron activation was successful via cFos marker
- We should expect (1) reduced apetite + (2) analgesic effect
- If we block opioid receptor agonist with naloxone, analgesic effect of beta-endorphin should go down

‘Rapid and robust increase in food intake in Tg POMC-ChR2 mice’

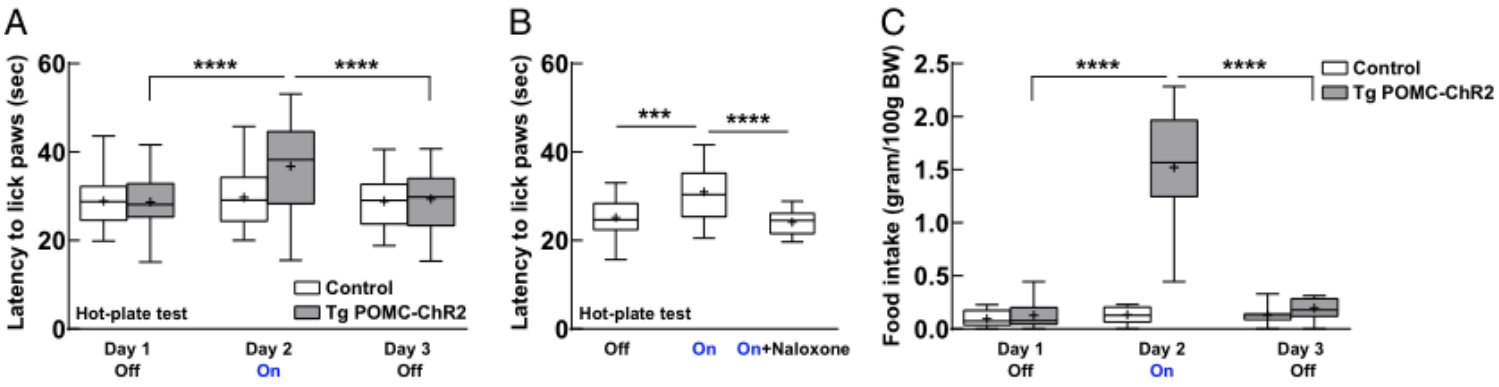


Fig. 4. Activation of Arc neurons derived from POMC-expressing lineage increases food intake in Tg POMC-ChR2 mice. (*A*) Repeated-measures two-way ANOVA revealed a significant genotype × day interaction, $F(2, 82) = 9.44$, $P < 0.001$, for the hot-plate test. Blue light stimulation of Arc neurons in Tg POMC-ChR2 mice led to an increased latency for the animals to lick their paws, $F(2, 52) = 21.91$, $P < 0.0001$; ****$P < 0.0001$; $n = 27$ mice. Latency for single transgenic littermate control mice without ChR2-eYFP expression to lick their paws was unchanged, $F(2, 30) = 1.06$, $P = 0.36$; $n = 16$ mice, 8 mice per single transgenic mouse line. (*B*) Increased latency induced by light stimulation in Tg POMC-ChR2 mice was reduced by pretreatment with opioid antagonist naloxone, $F(2, 24) = 15.2$, $P < 0.0001$; ***$P < 0.001$, ****$P < 0.0001$; $n = 13$ mice. (*C*) Repeated-measures two-way ANOVA revealed a significant genotype × day interaction, $F(2, 54) = 76.59$, $P < 0.0001$, for the food intake study. Light stimulation of Arc neurons evoked a robust increase in food intake in Tg POMC-ChR2 mice, $F(2, 24) = 68.28$, $P < 0.0001$; ****$P < 0.0001$; $n = 13$ mice. Food intake for control mice was unchanged following light stimulation of Arc, $F(2, 30) = 1.19$, $P = 0.32$; $n = 16$ mice. Box plots show median, mean (+), lower and upper quartiles (boxes), and minima and maxima (whiskers).