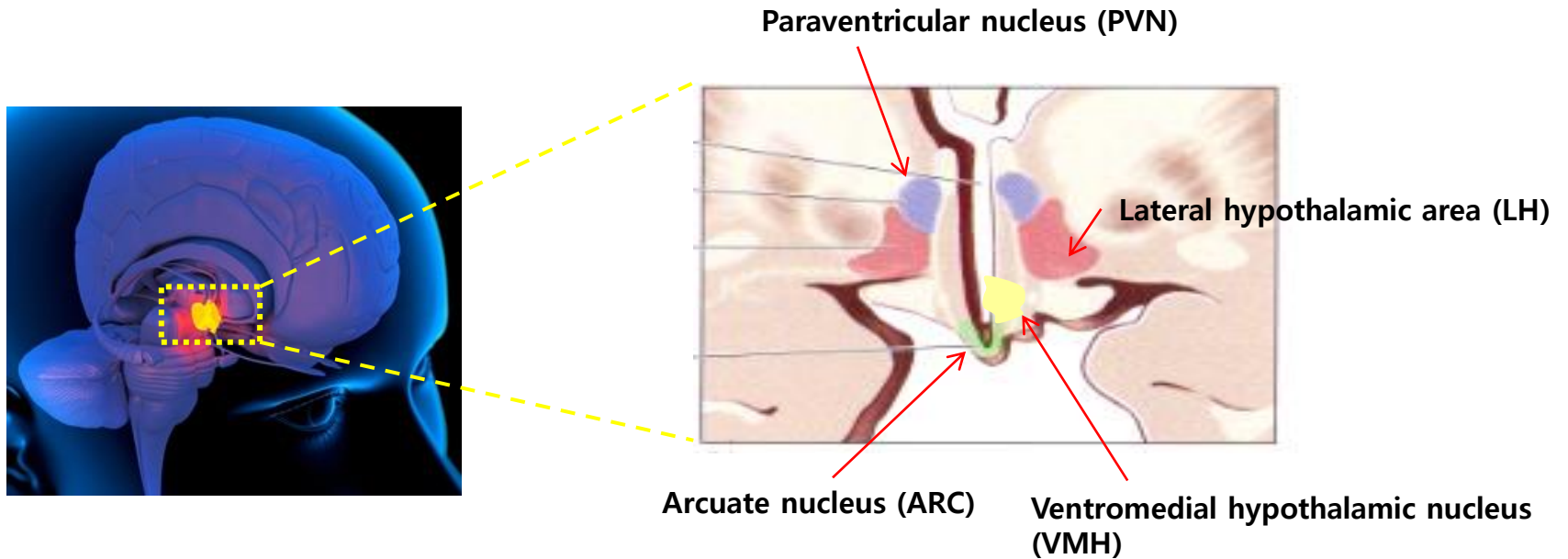


Potential impacts of hypothalamic glial cells in the regulation of energy homeostasis

Jae Geun Kim Ph.D.
Incheon National University

Hypothalamus as a central unit for the regulation of homeostasis



Control of endocrine system

Temperature regulation

Circadian rhythm

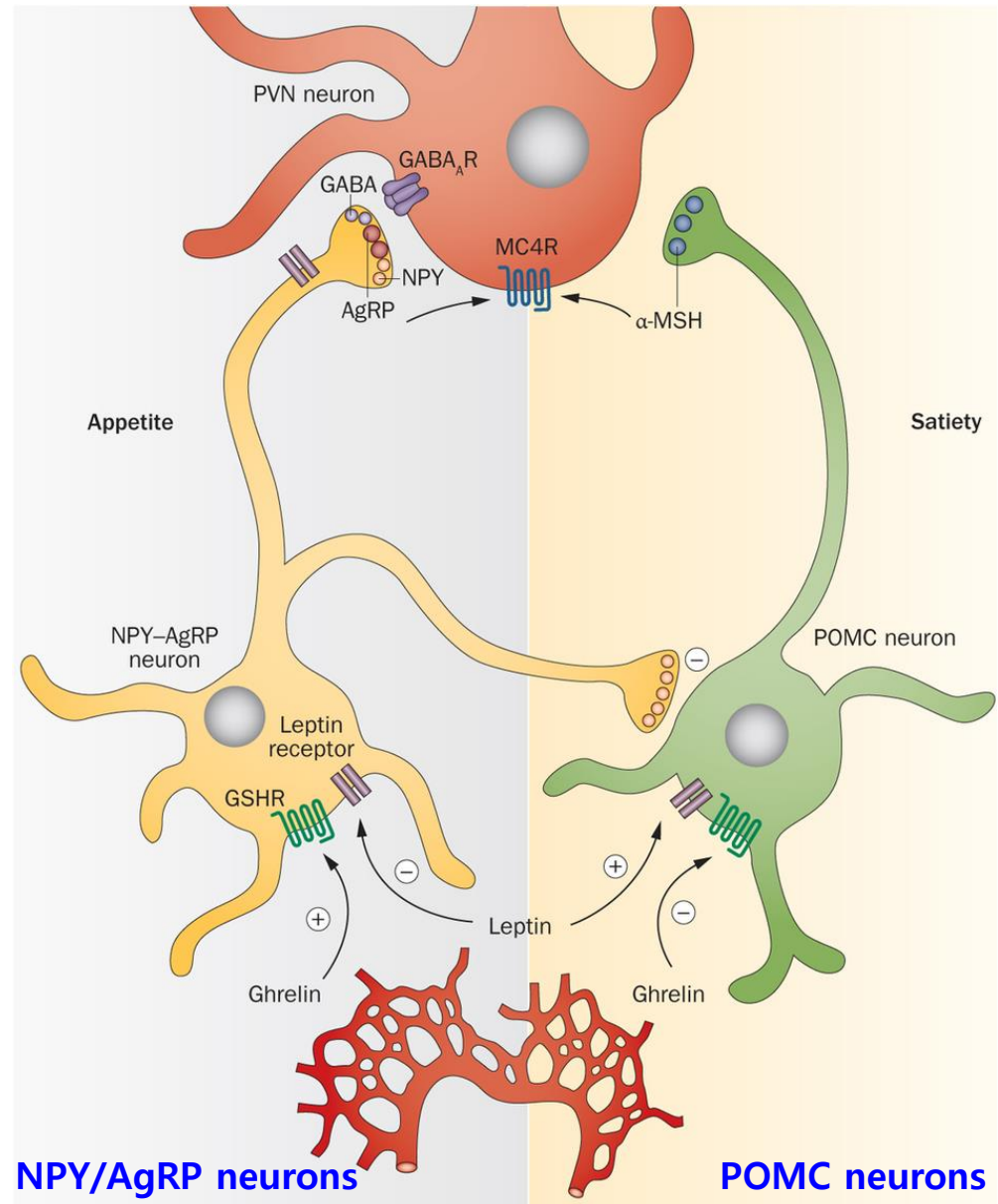
Sleep regulation

Energy homeostasis

Distinct neuronal population for the control of appetite in the hypothalamic arcuate nucleus

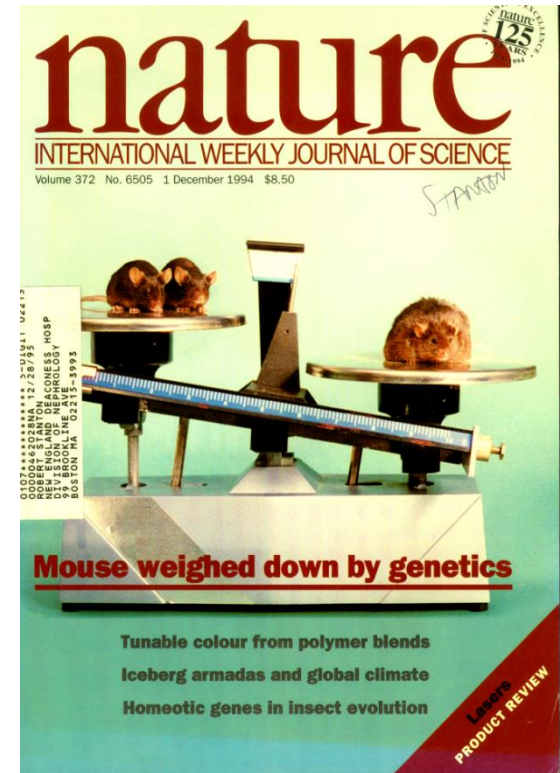
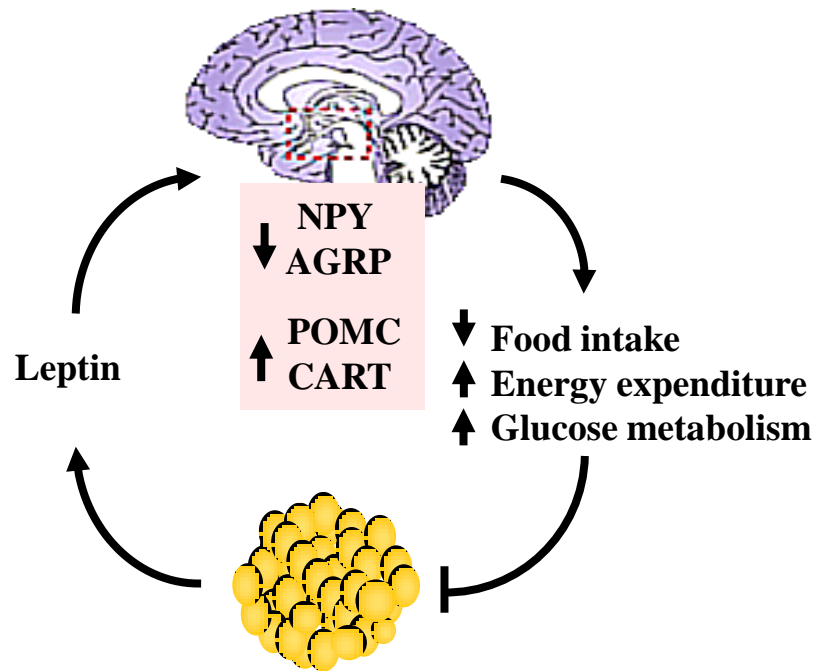
AgRP (Hunger promoting)

POMC (Satiety promoting)



Leptin

- A hormone that inhibits feeding
- Secreted from adipose tissue and circulated through whole body
- Blood level of leptin is proportional to adiposity and body weight (BMI)
- Long form leptin receptor (ObRb) is strongly expressed in hypothalamus



1st of December, 1994

Discovery of obese gene

Leptin deficiency in human and mouse

Human patient
(Leptin deficient)



Leptin replacement



Ob/Ob mouse



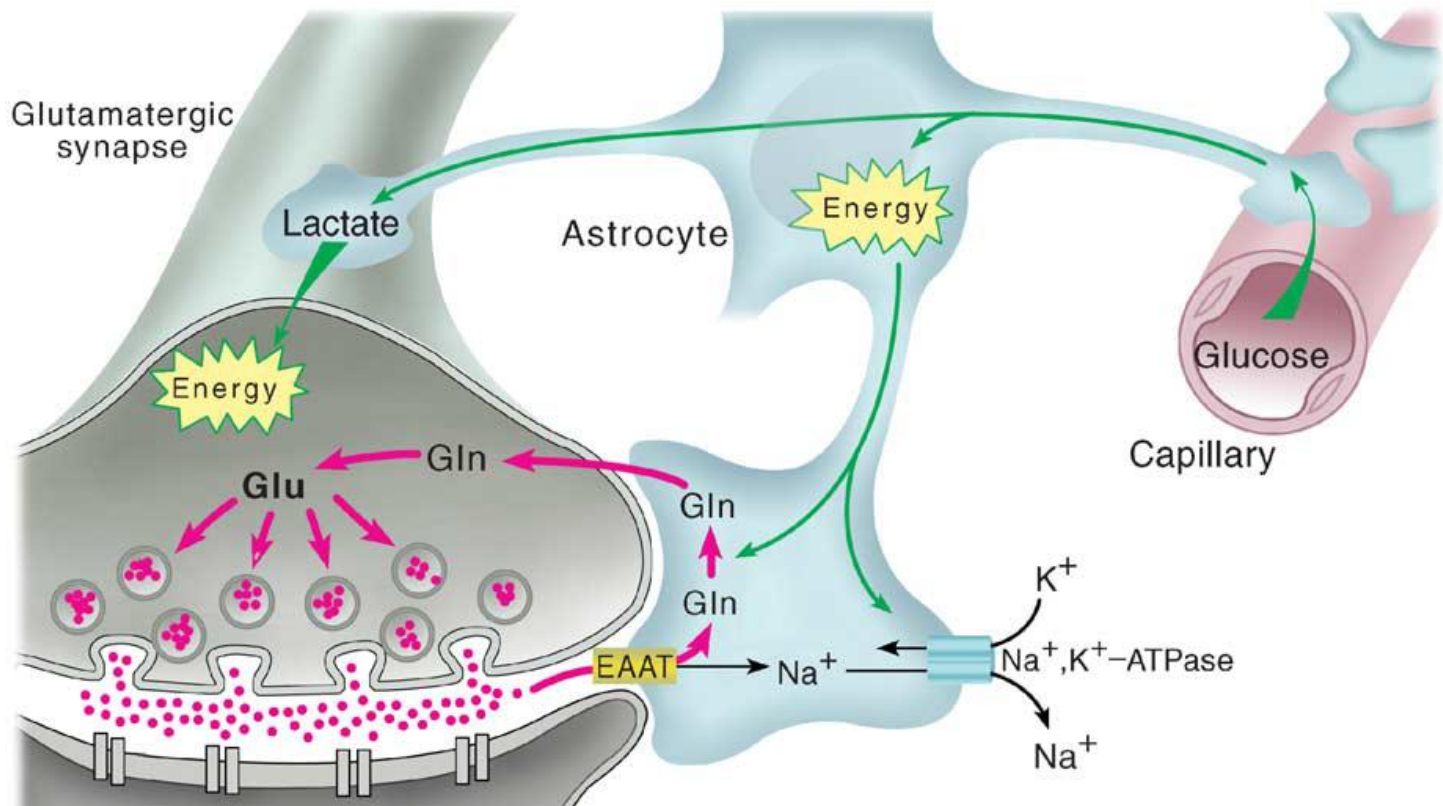
1986

Lep^{ob}

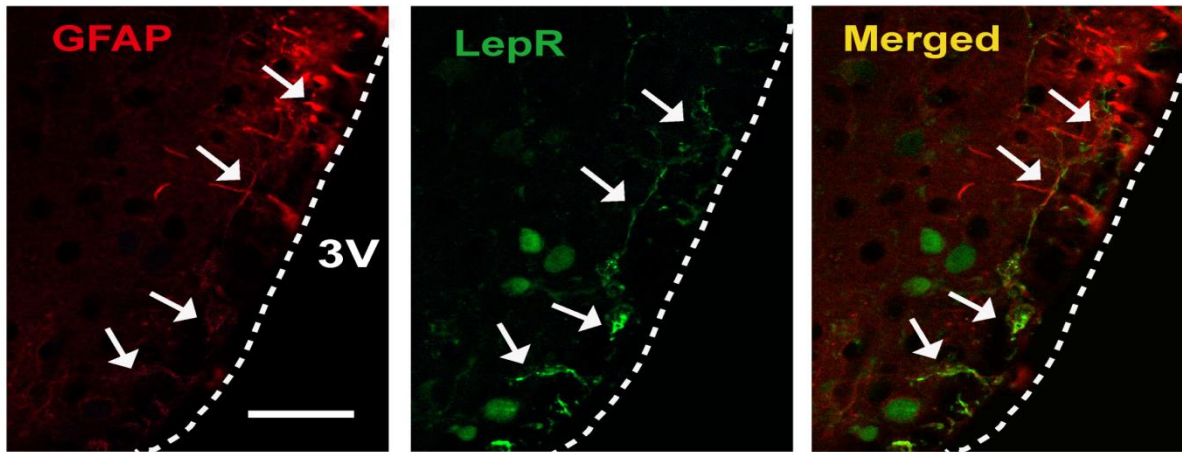
Astrocyte

Supports neuronal homeostasis

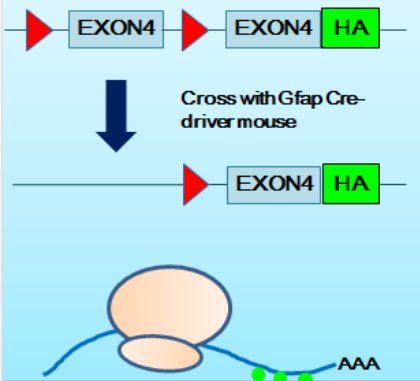
- Providing nutrients from capillary to neurons
- Regulating neurotransmitter homeostasis in the synaptic cleft area



Presence of leptin receptors in the hypothalamic astrocytes

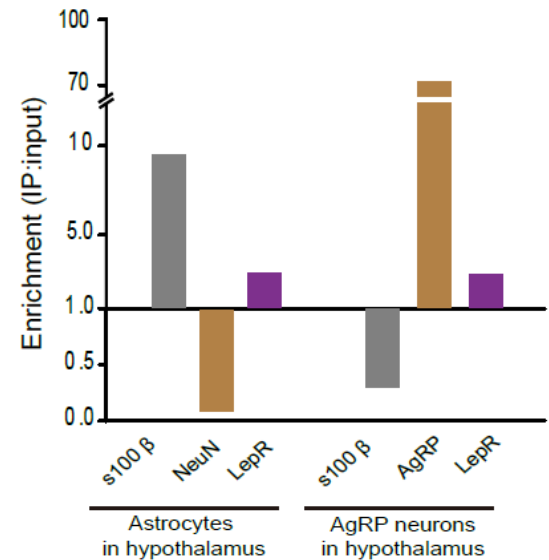
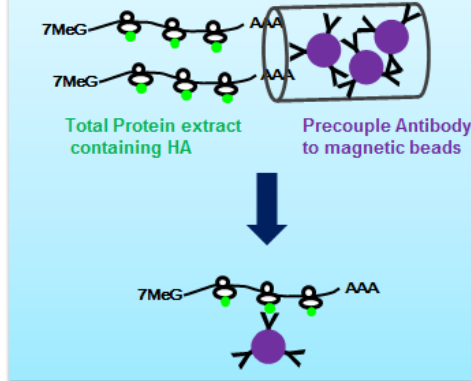


Model: Rpl22 floxed:Gfap cre



Homogenization

Immunoprecipitation



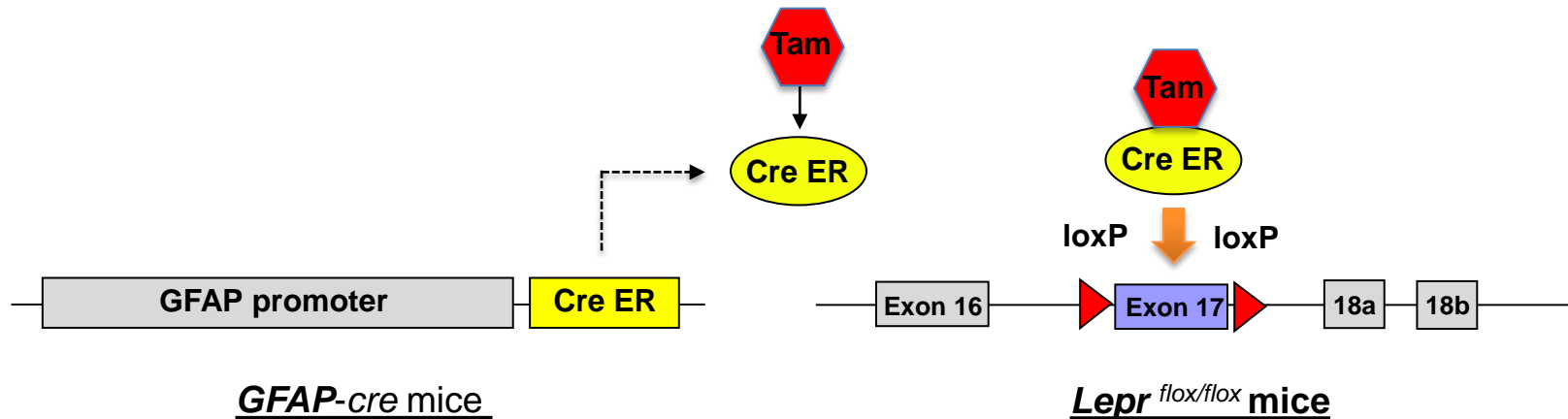
Question 1

Does leptin receptor signaling in the hypothalamic astrocytes affect whole body energy metabolism?

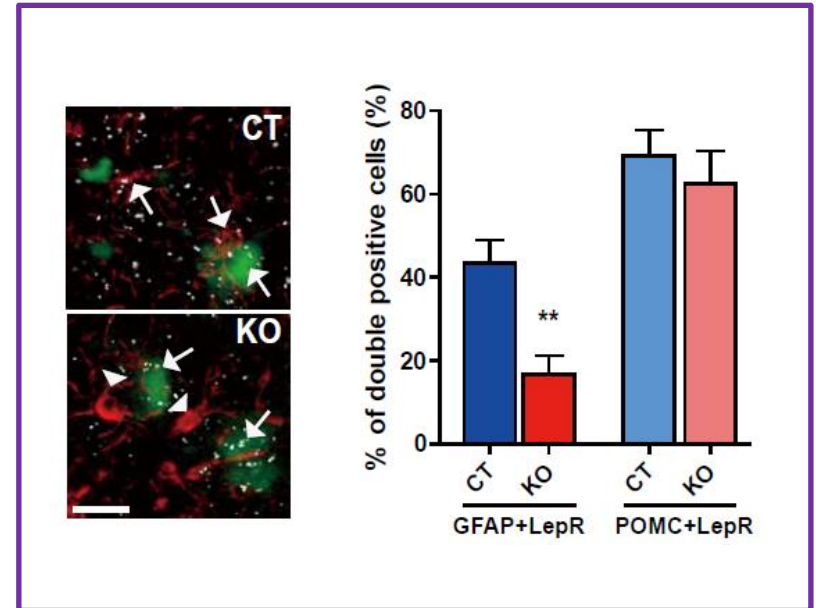
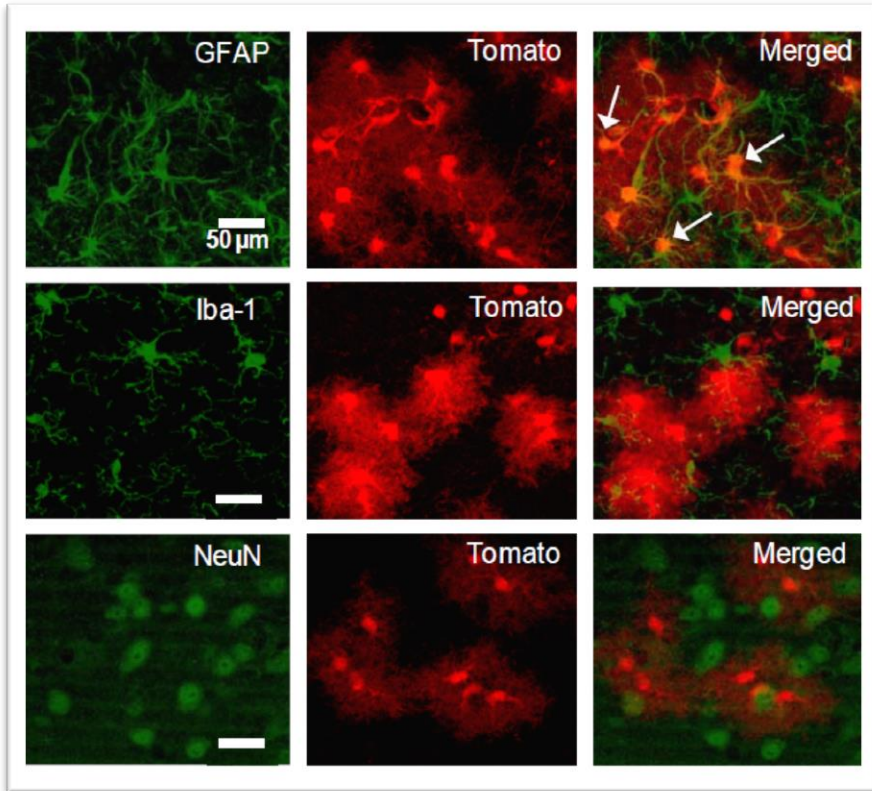
Animal model: Impaired leptin receptor (Lepr) signaling in astrocytes

Animal model: Cre^{ERT2}/ loxP system

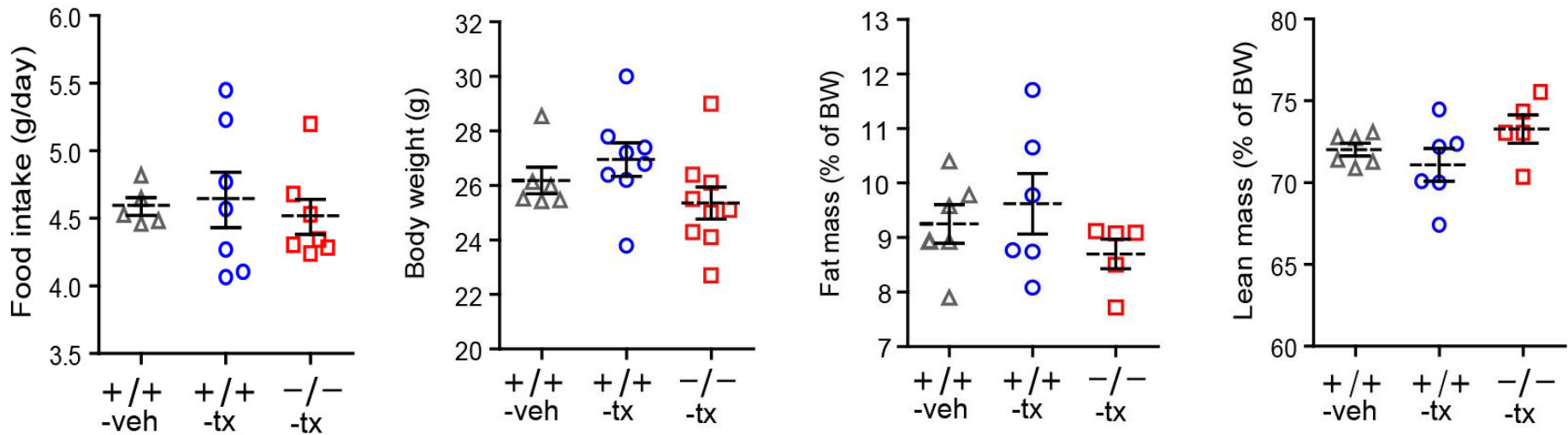
➔ Tamoxifen-injection at 5 weeks after birth



Verification of the astrocyte-specific deletion of leptin receptor

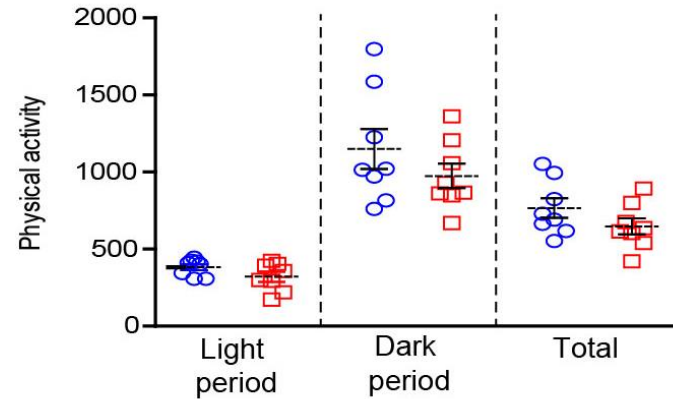
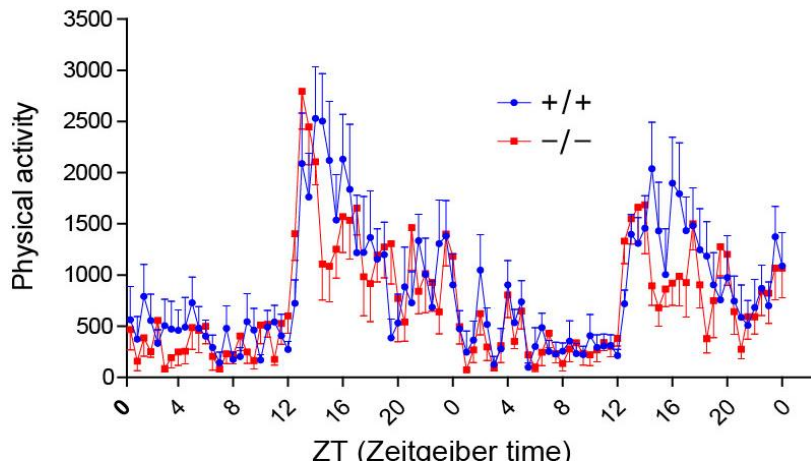
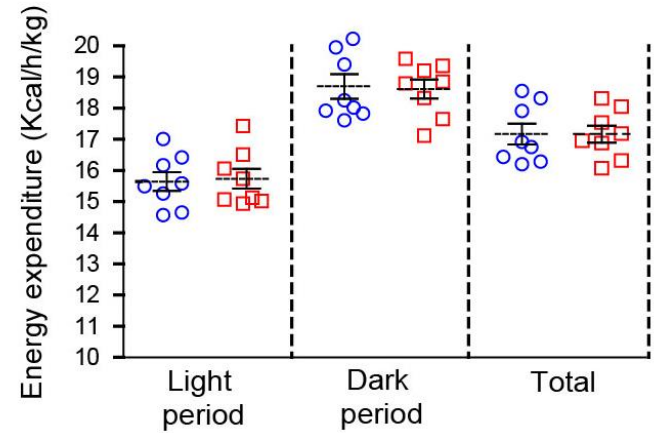
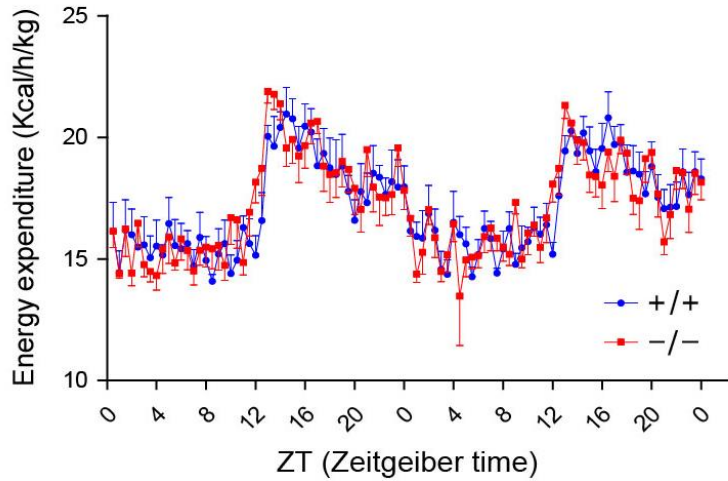


Metabolic phenotypes in the *Gfap-Lepr^{+/+}* and *Gfap-Lepr^{-/-}* mice

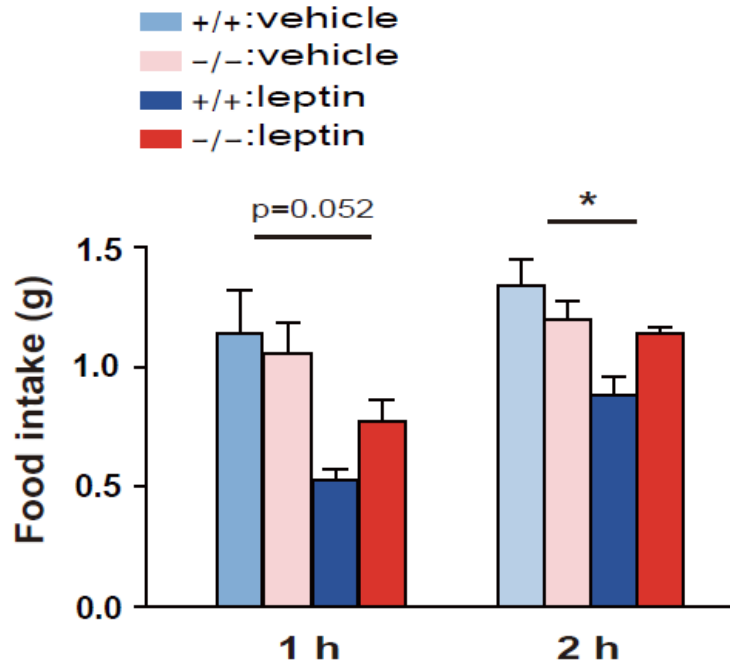


+/+ - veh : Wild Type + vehicle
+/+ - tx : Wild Type + Tamoxifen
-/- - tx : *Lepr:Gfap* KO + Tamoxifen

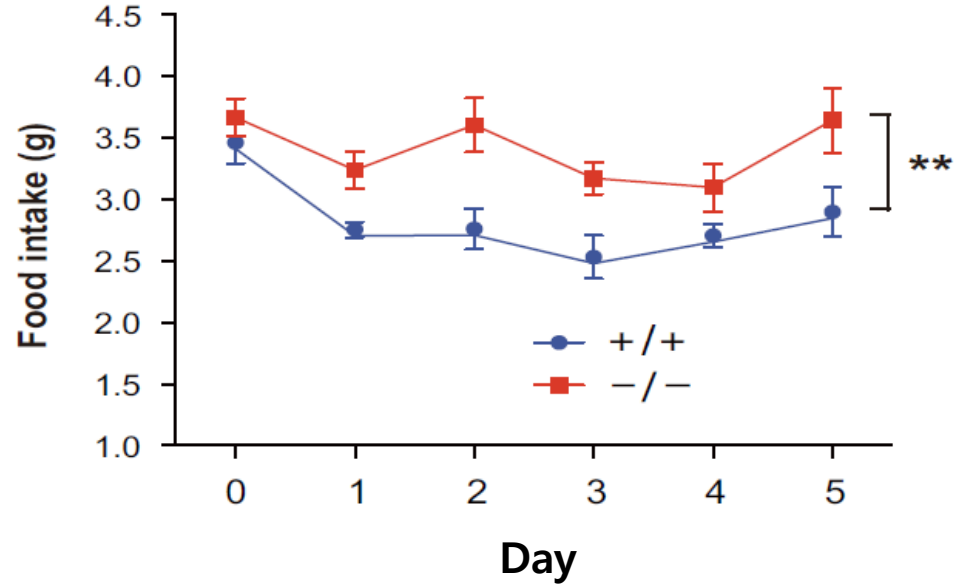
Energy expenditure and physical activity in the *Gfap-Lepr^{+/+}* and *Gfap-Lepr^{-/-}* mice



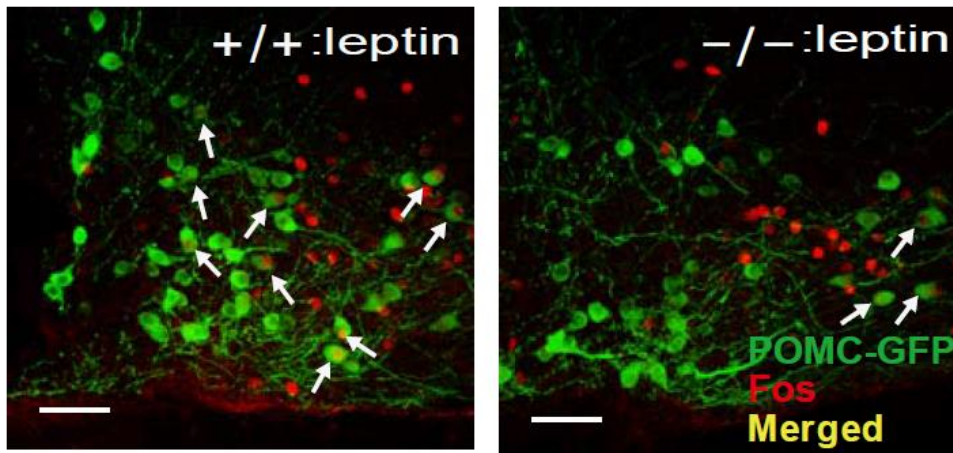
Impaired leptin receptor signaling in astrocytes blunts leptin-induced anorexia



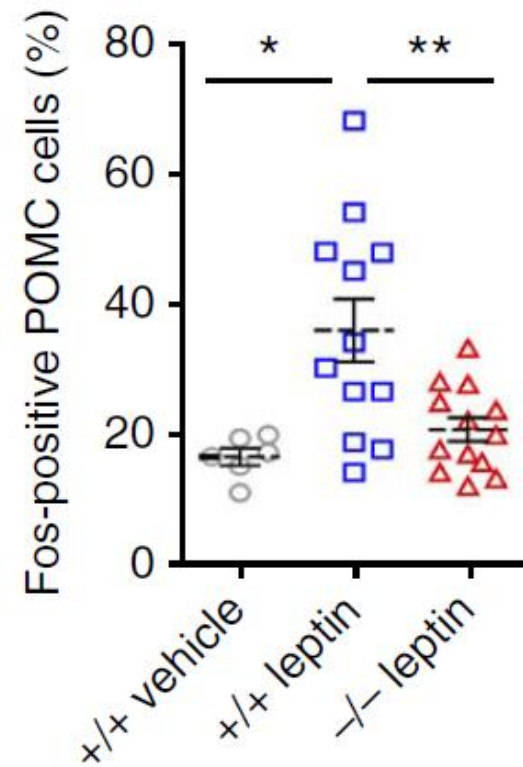
+/+ : Wild Type
-/- : *Lepr:Gfap* KO mice



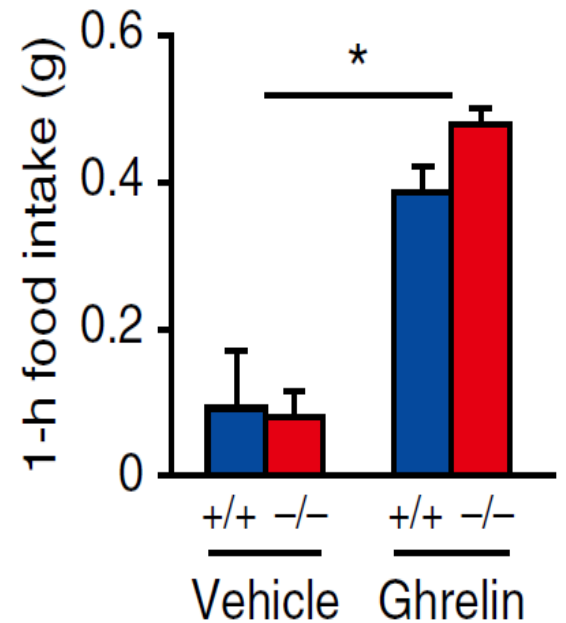
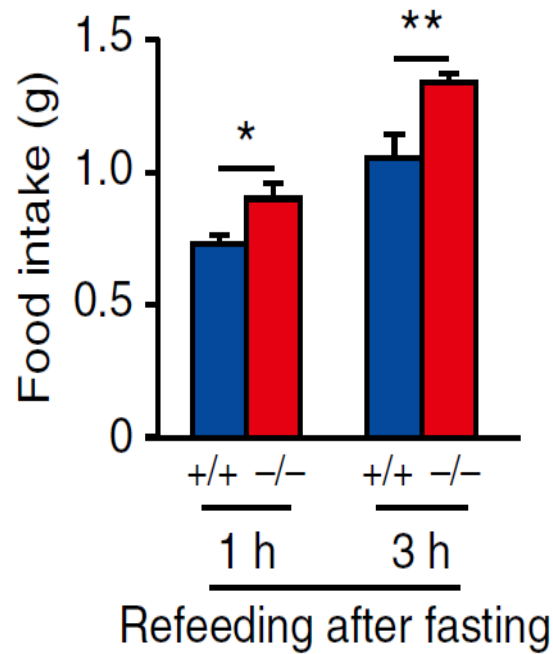
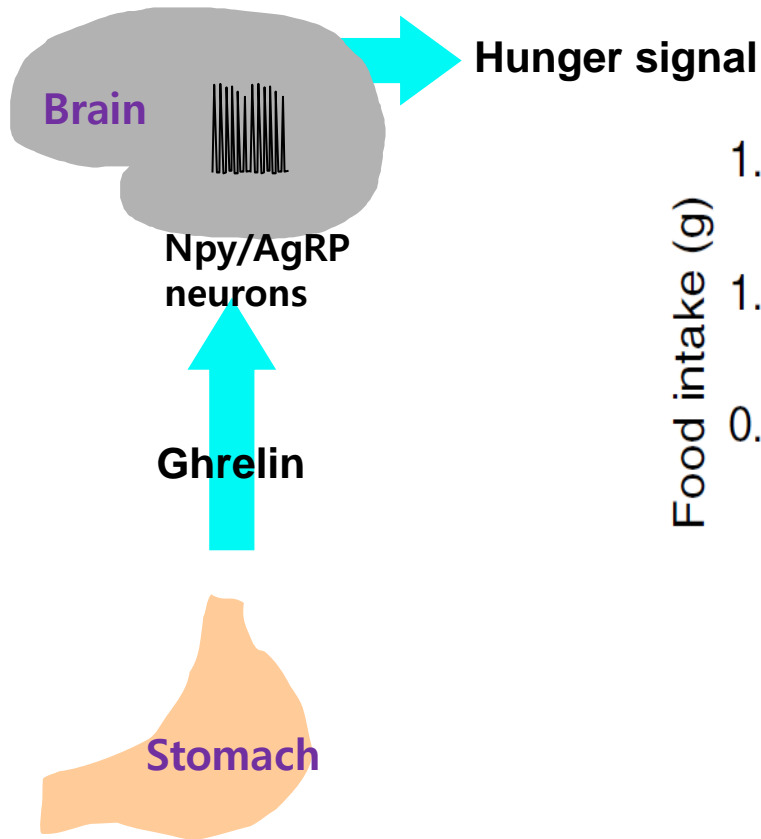
Number of leptin-induced cFos-positive POMC cells was reduced in *Gfap-Lepr^{-/-}* mice



c-Fos: Marker for neuronal activity

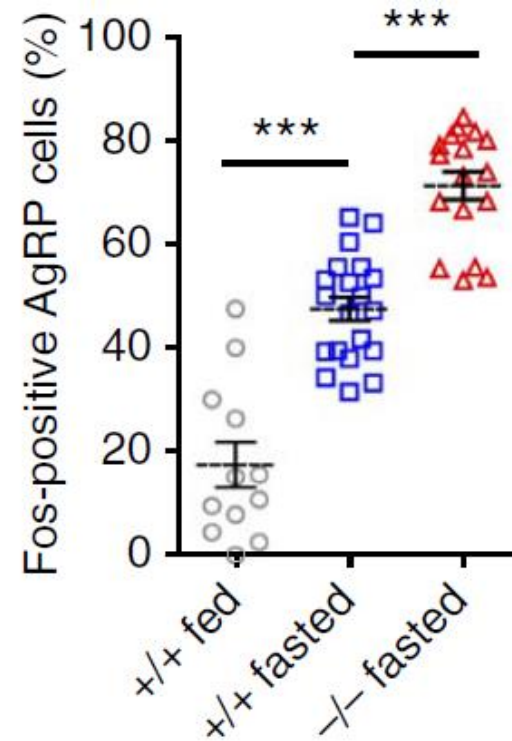
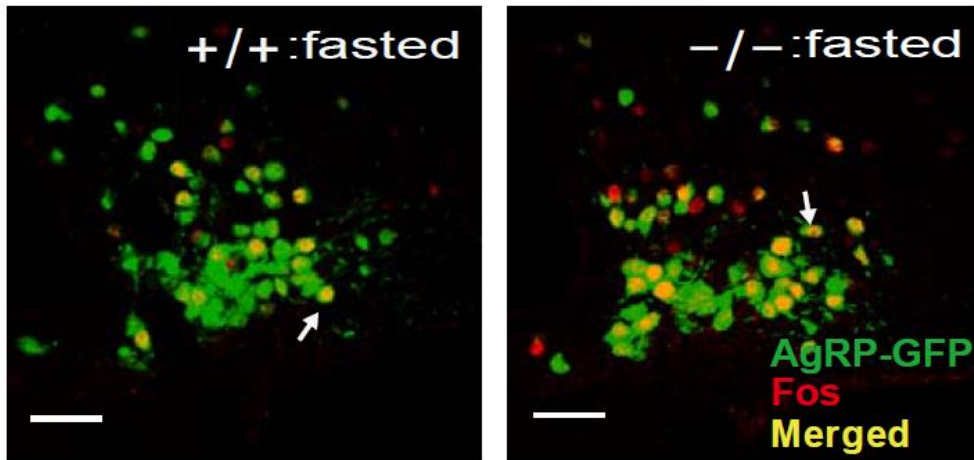


Impaired leptin receptor signaling in astrocytes enhances fasting- or ghrelin-induced hyperphagia



+/+ : Wild Type
-/- : *Lepr:Gfap* KO mice

Number of Fos-positive AgRP cells induced by overnight fasting was enhanced in *Gfap-Lepr^{-/-}* mice

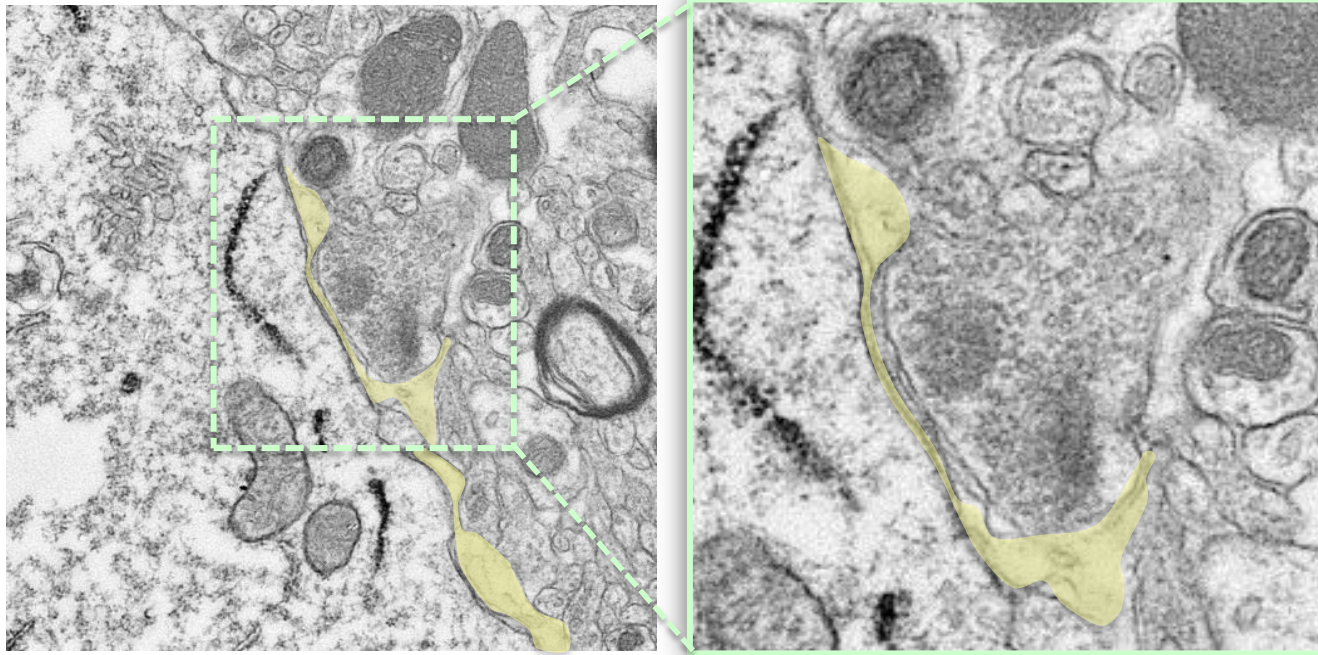


Question 2

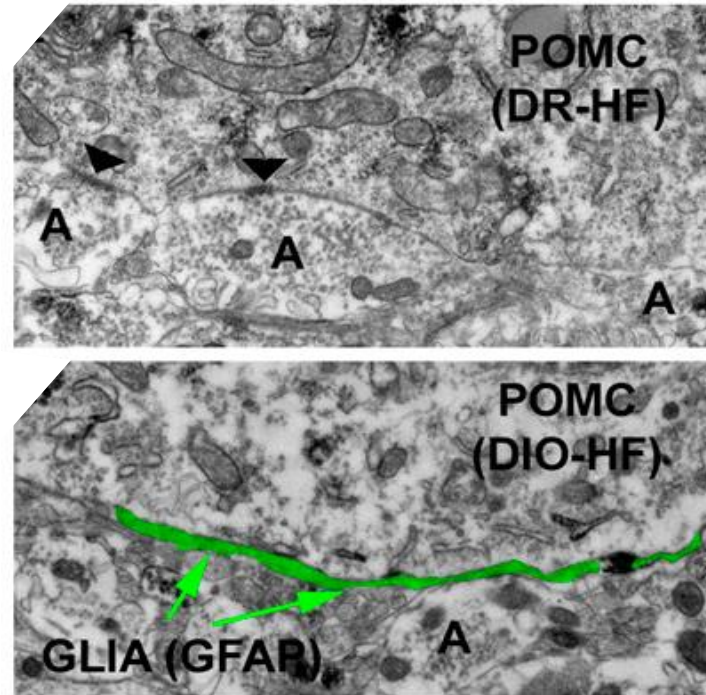
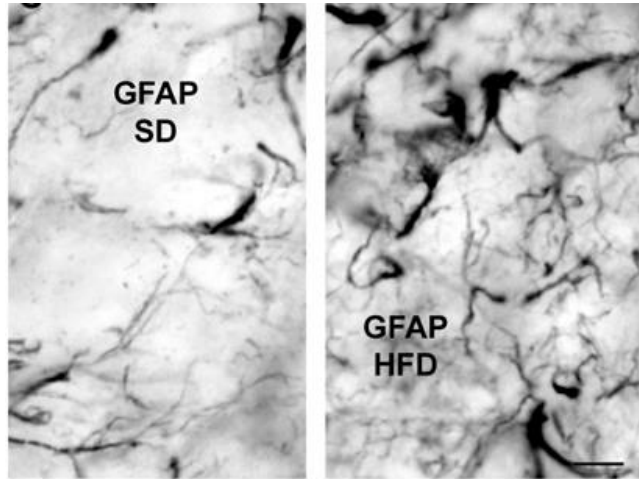
Do astrocytes modulate synaptic remodeling and transmission in the hypothalamic neuronal circuit regulating energy metabolism?

Key histological finding to establish the hypothesis:

Possible function of glial coverage onto the perikarya membrane of neurons



Astrocytic process onto perikarya membrane of neurons physically controls synaptic formation onto hypothalamic POMC neurons



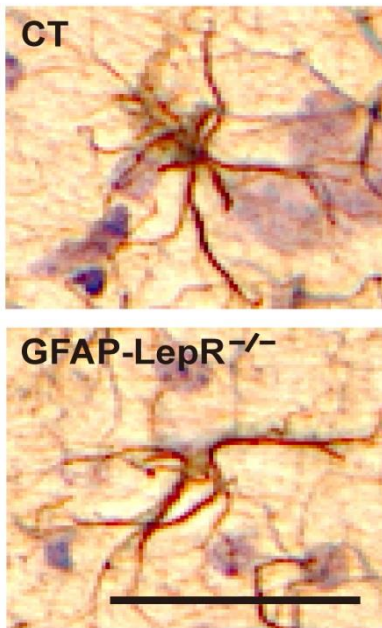
Key histological findings

Over-nutrition (High Fat Diet)

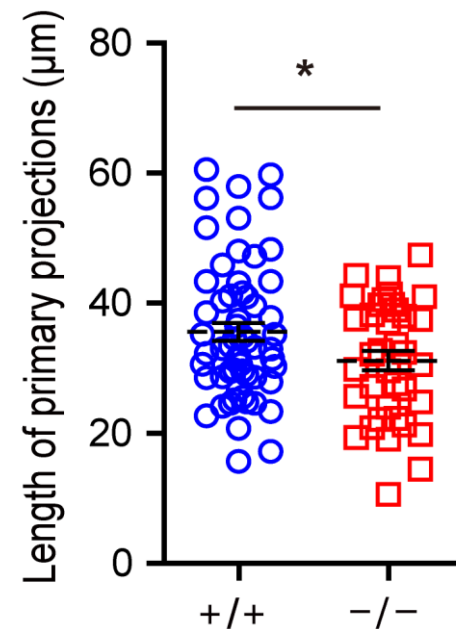
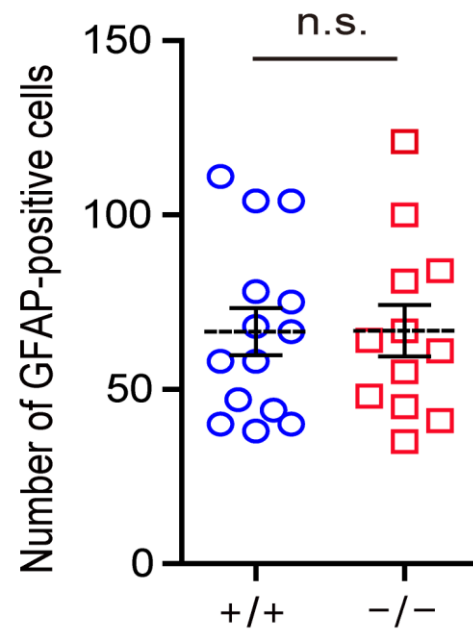


- Gliosis (Enhanced primary projections)
- Extended astrocyte coverage
- Reduced synaptic proteins

Cell autonomous impairment of leptin receptor signaling alters astrocyte morphology



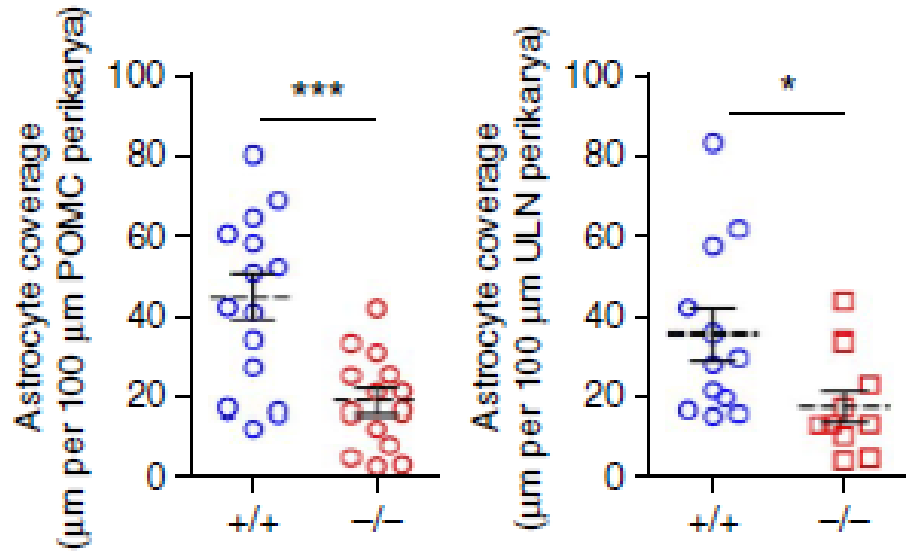
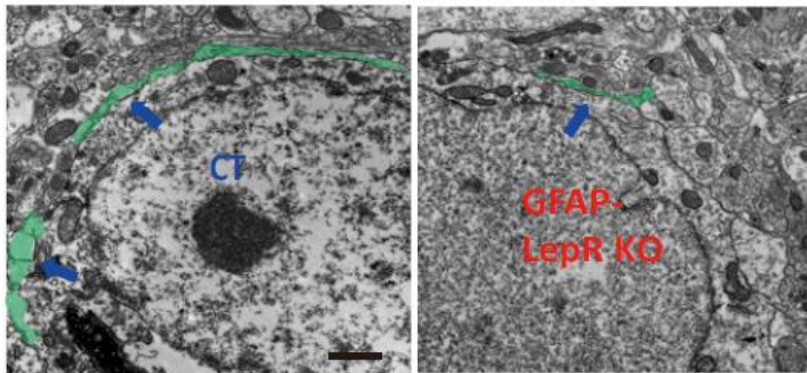
+/+ : Wild Type
-/- : *Lepr:Gfap* KO mice



Cell autonomous impairment of leptin receptor (Lepr) signaling reduces astrocytic coverage onto melanocortin cells.

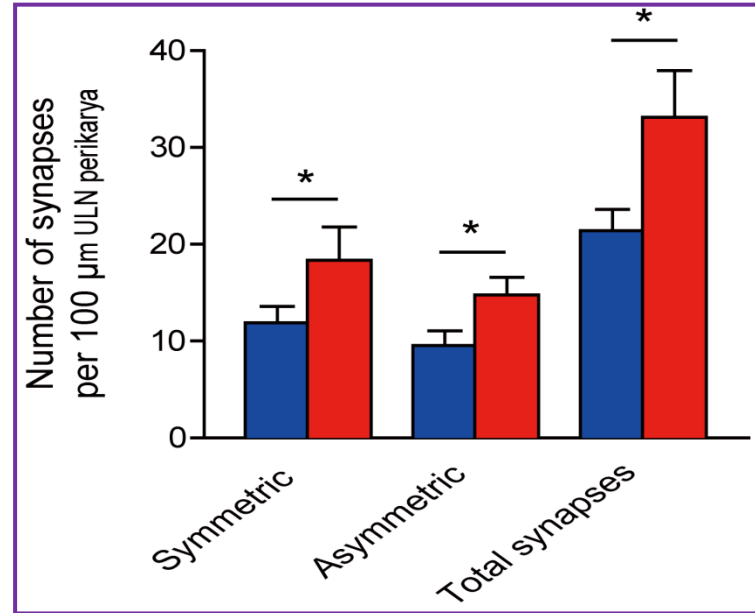
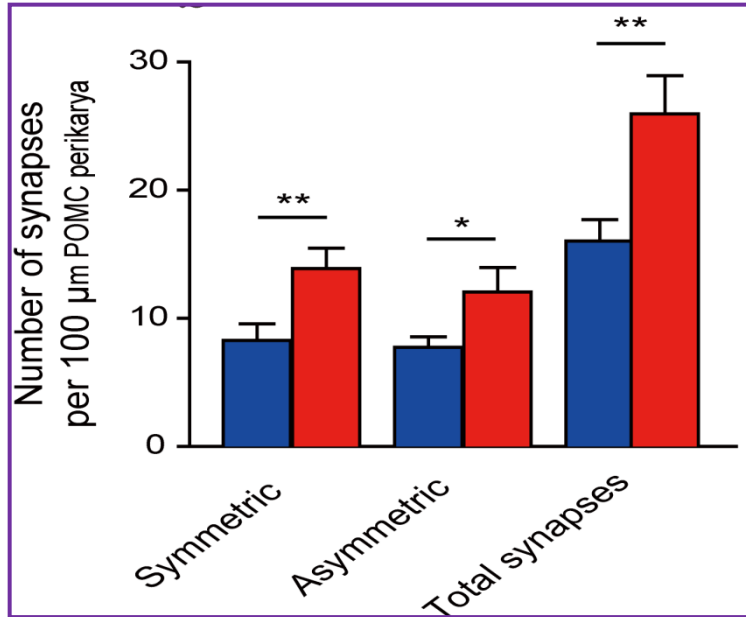
Gfap-Lepr^{+/+}

Gfap-Lepr^{-/-}

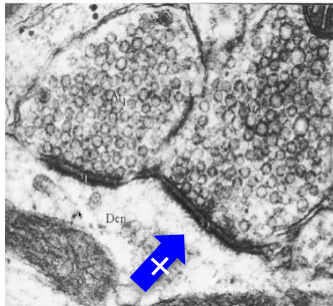


+/+ : Wild Type
-/- : *Lepr:Gfap* KO mice

Impaired leptin receptor signaling in astrocytes increases the number of synapses onto POMC and AgRP neurons.



Asymmetric
(Excitatory synapse)



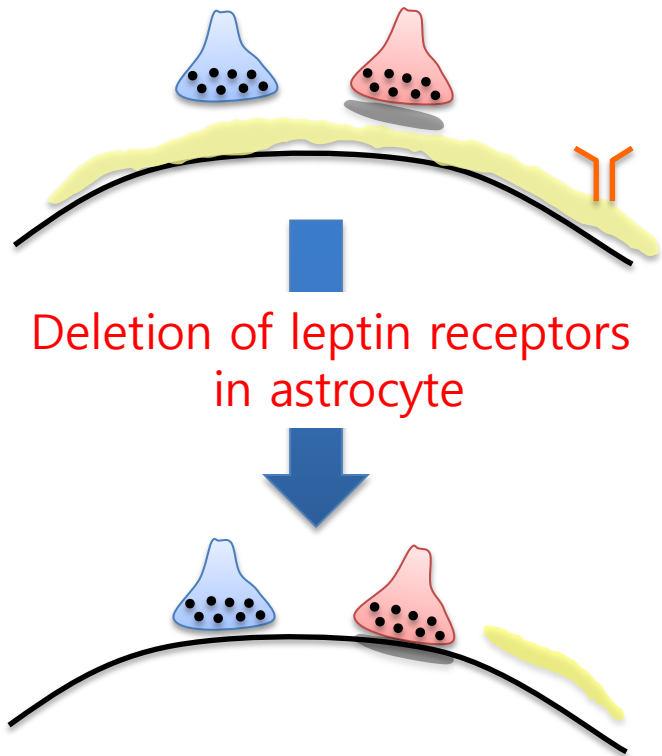
Symmetric
(Inhibitory synapse)



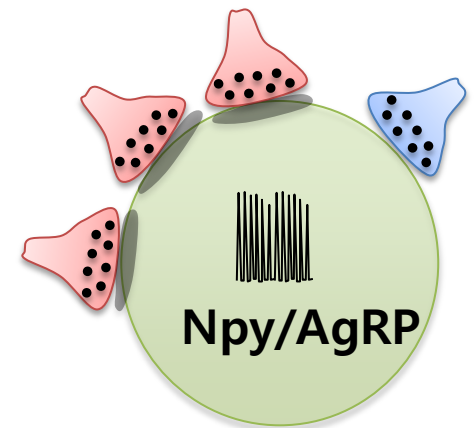
■ : Wild Type
■ : *Lepr:Gfap* KO mice

Summary of cellular mechanism

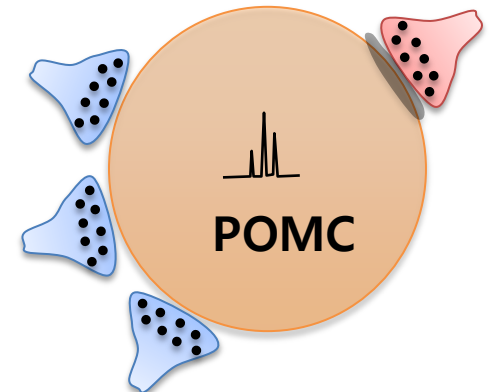
Astrocytes participate in the synaptic input of melanocortin cells triggered by leptin



Hunger signals
(Ghrelin)



Satiety signals
(Leptin)



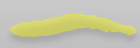
ObRb



Inhibitory synapse



Excitatory synapse

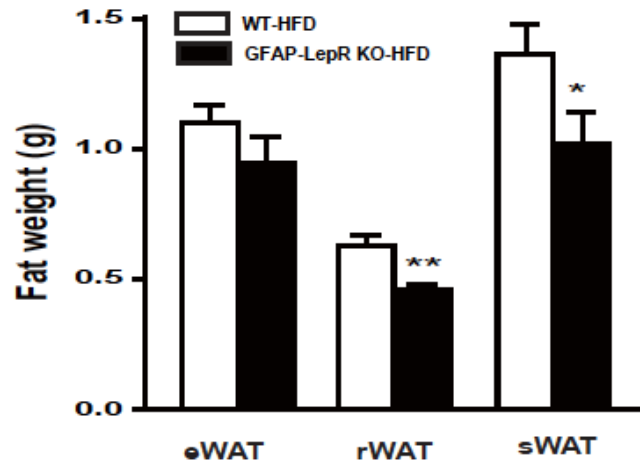
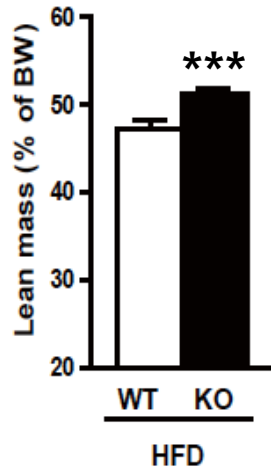
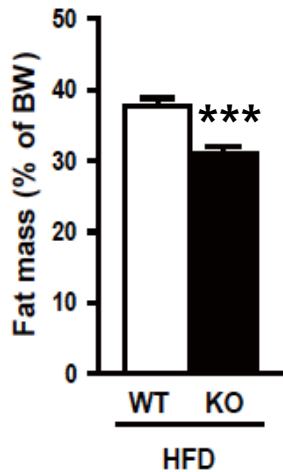
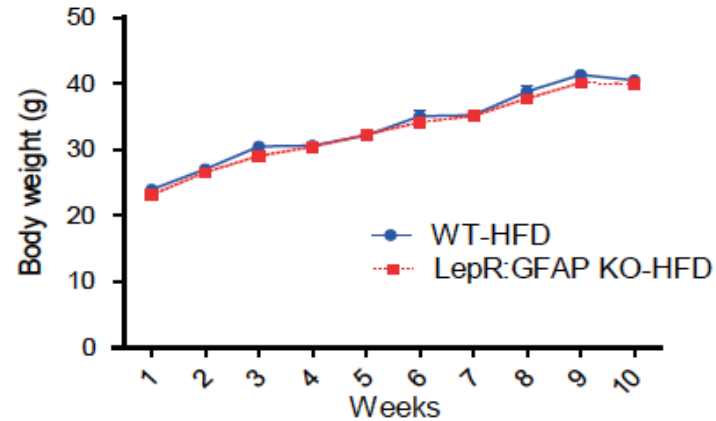
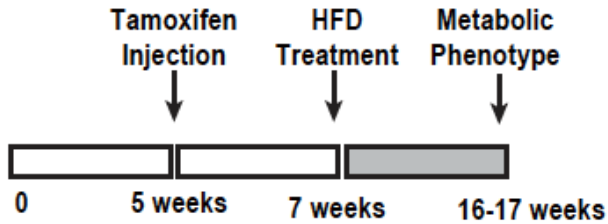


Astrocyte process

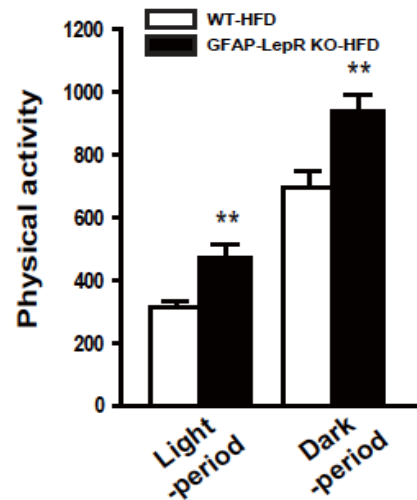
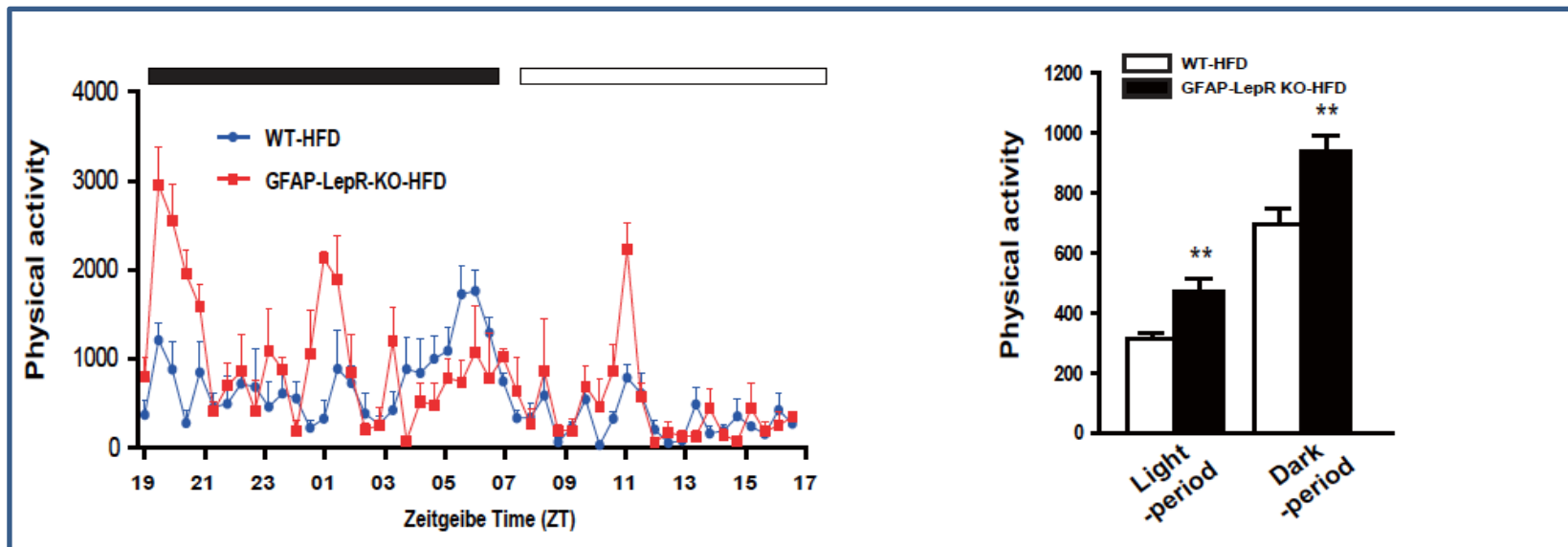
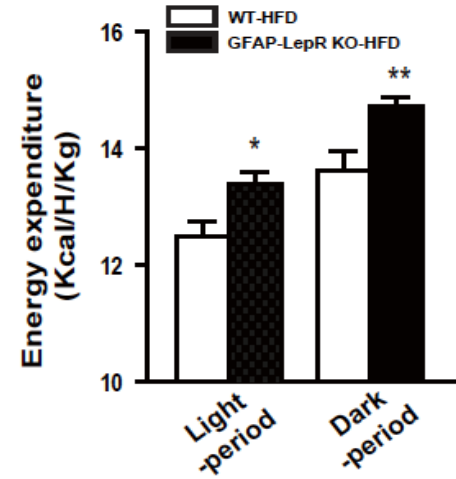
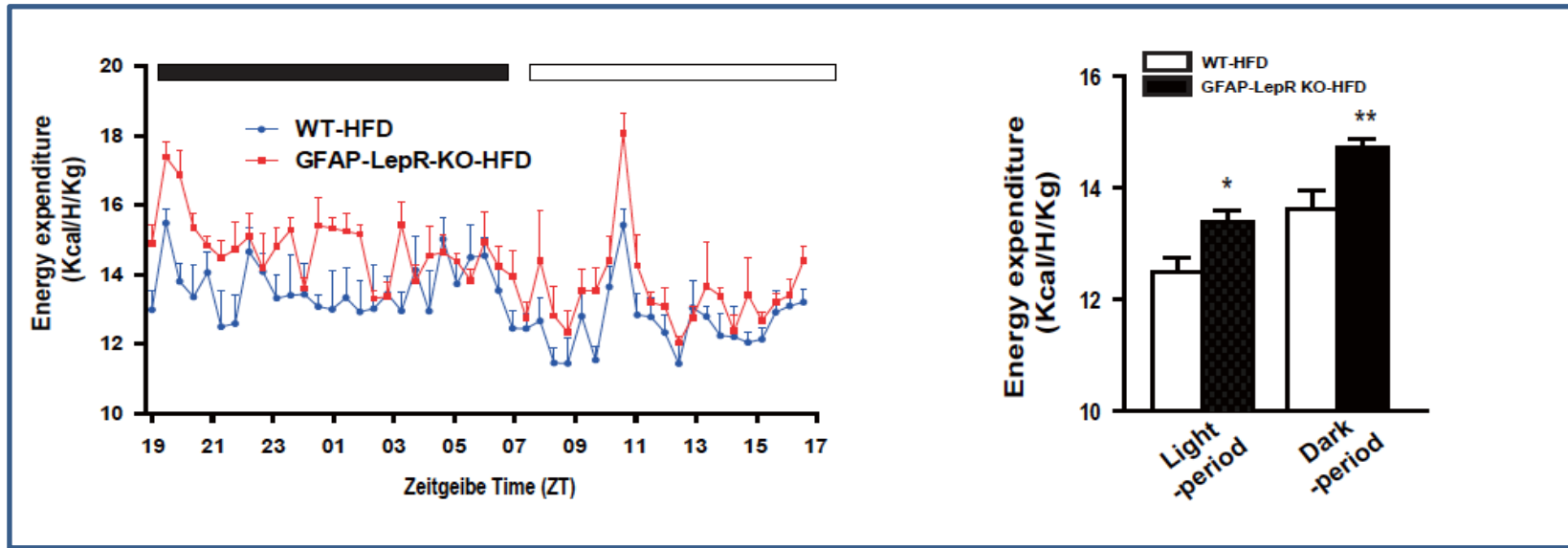
Question 3

Do the *Gfap-Lepr^{-/-}* mice display altered metabolic phenotypes in High Fat Diet treatment ?

Impaired leptin receptor signaling in astrocytes protects mice from obesity induced by high fat diet treatment

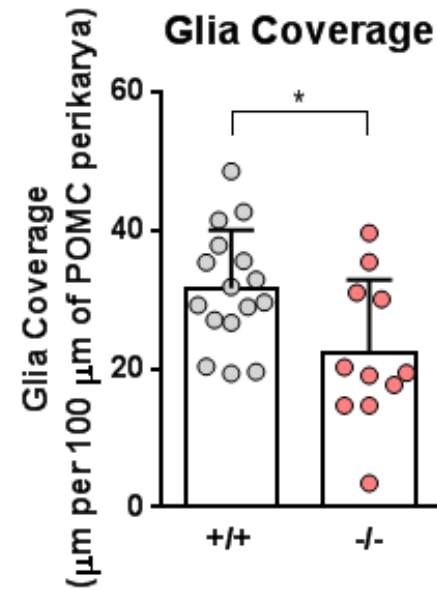
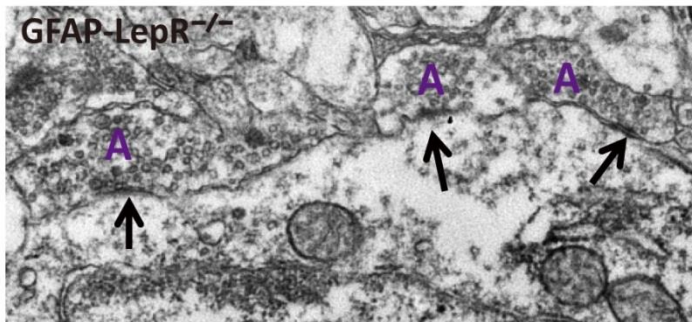
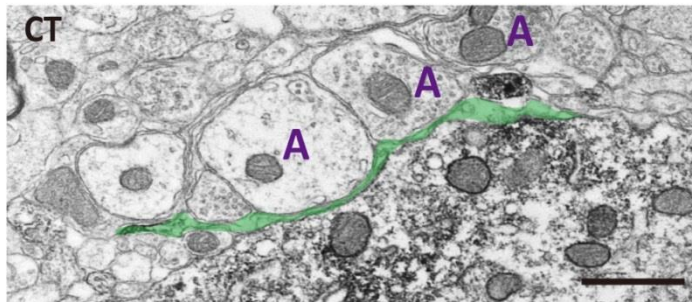


Impaired leptin receptor signaling in astrocytes triggers enhanced energy expenditure in an overnutrition condition



Unpublished data

Elevated glial coverage onto HFD-treated hypothalamic neurons was reduced in *Gfap-Lepr*^{-/-} mice

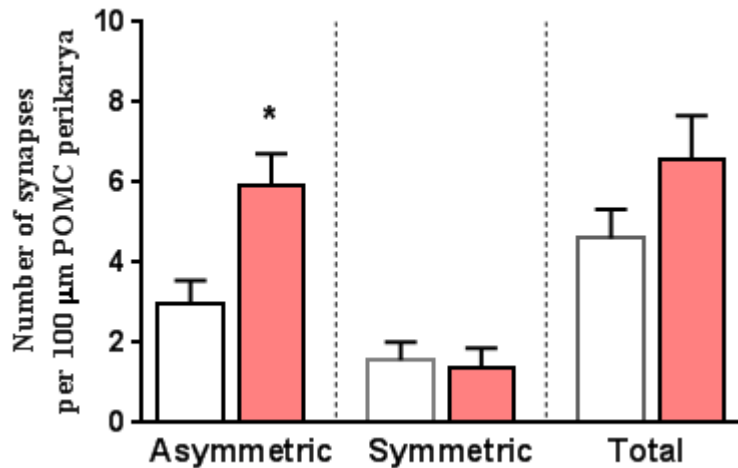


+/+ : Wild Type

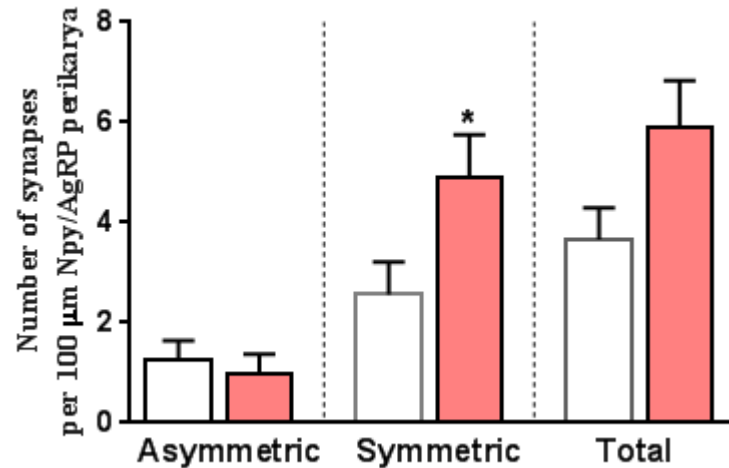
-/- : *Lepr:Gfap* KO mice

Selective recruitment of synapses onto hypothalamic neurons in response to HFD treatment might be related to improved obesity phenotypes seen in *Gfap-Lepr^{-/-}* mice.

POMC neurons in HFD



NPY/AgRP neurons in HFD



□ : Wild Type
■ : *Lepr:Gfap* KO mice

Summary and Further studies

- ➔ Astrocytes modulate synaptic remodeling and transmission in the hypothalamic neuronal circuit regulating energy metabolism.
- ➔ Impaired leptin receptor signaling in astrocytes improves obesity induced by high fat diet treatment.
- ➔ This effect is mediated, at least in part, via selective regulation of synaptic input organization onto hypothalamic neurons to trigger homeostatic energy balance from HFD-induced obesity.

Acknowledgment

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Byung Ju Lee, PhD (University of Ulsan, Dept. of Biological Sciences)

Sungho Jin, PhD student (University of Ulsan, Dept. of Biological Sciences)

Marco Koch, PhD (University of Leipzig , Germany)



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