Role of Hypothalamic Tanycytes in Metabolic Homeostasis

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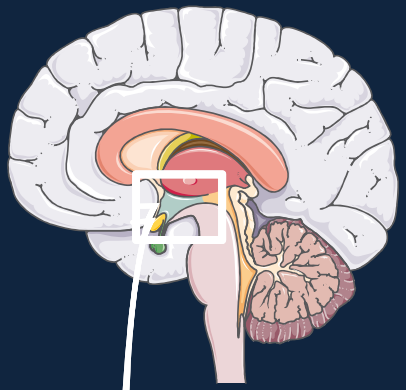
France

Conflict of interest disclosure

None

Metabolic signals and energy homeostasis

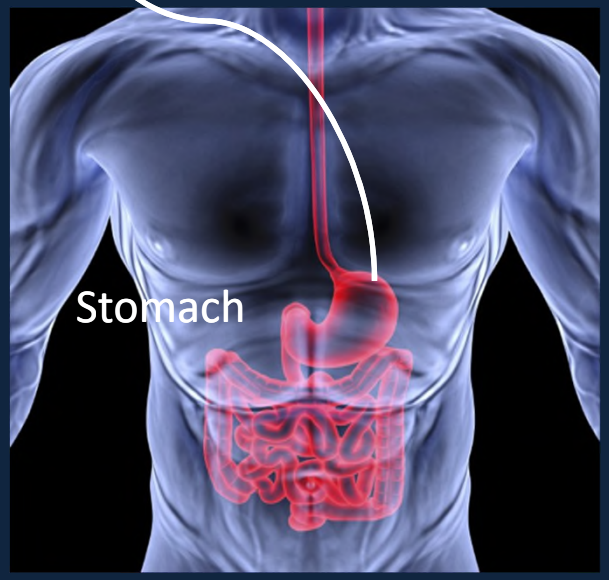
CNS:
hypothalamus



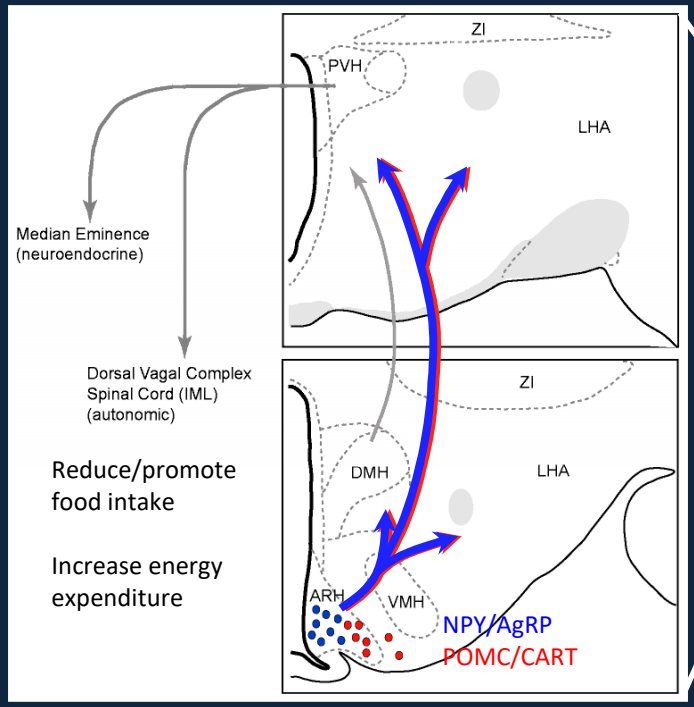
Ghrelin

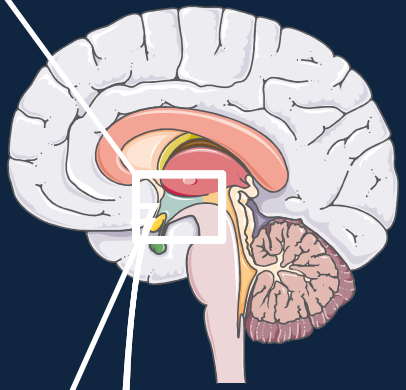
Leptin

Adipocytes



Metabolic signals and energy homeostasis





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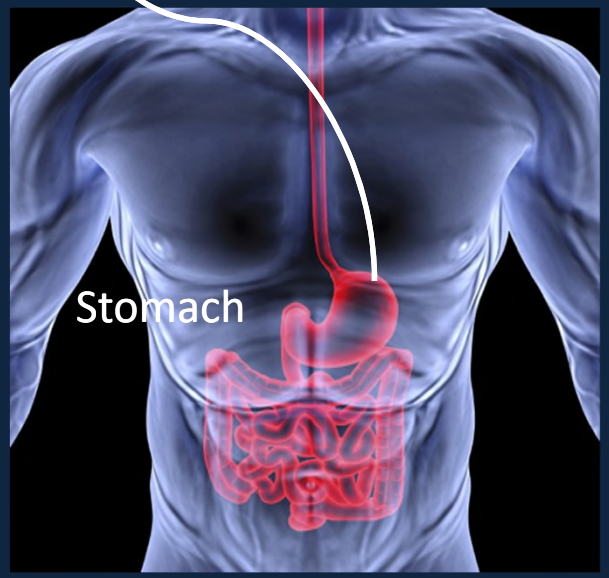
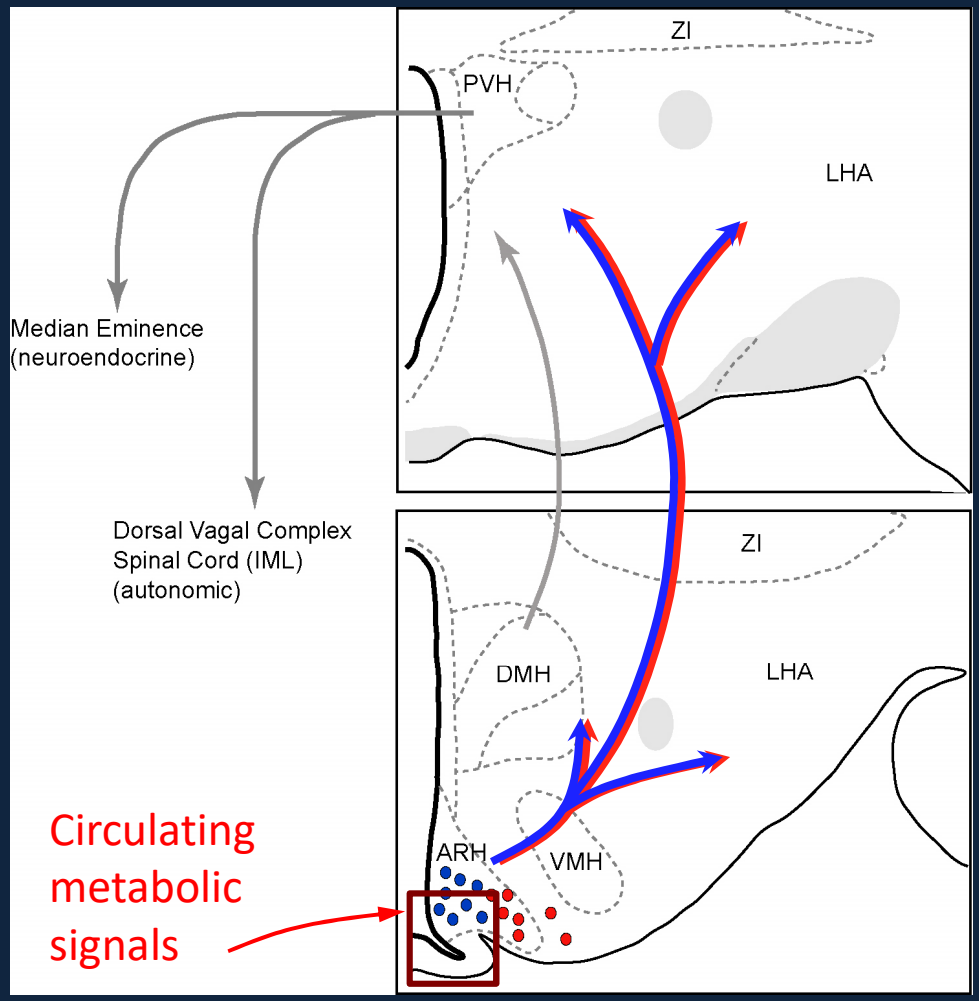
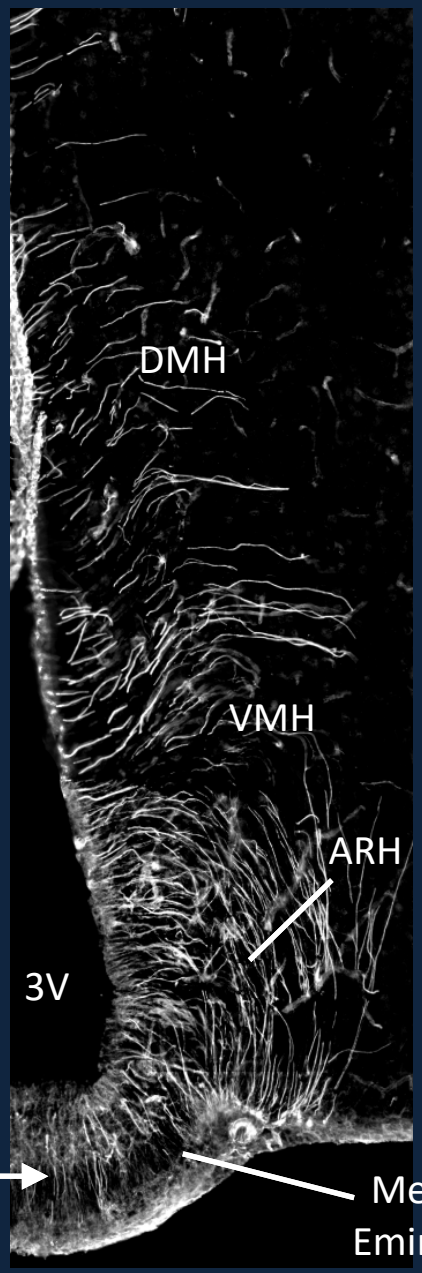


Do circulating metabolic signals have direct access to the arcuate nucleus of the hypothalamus (ARH)?





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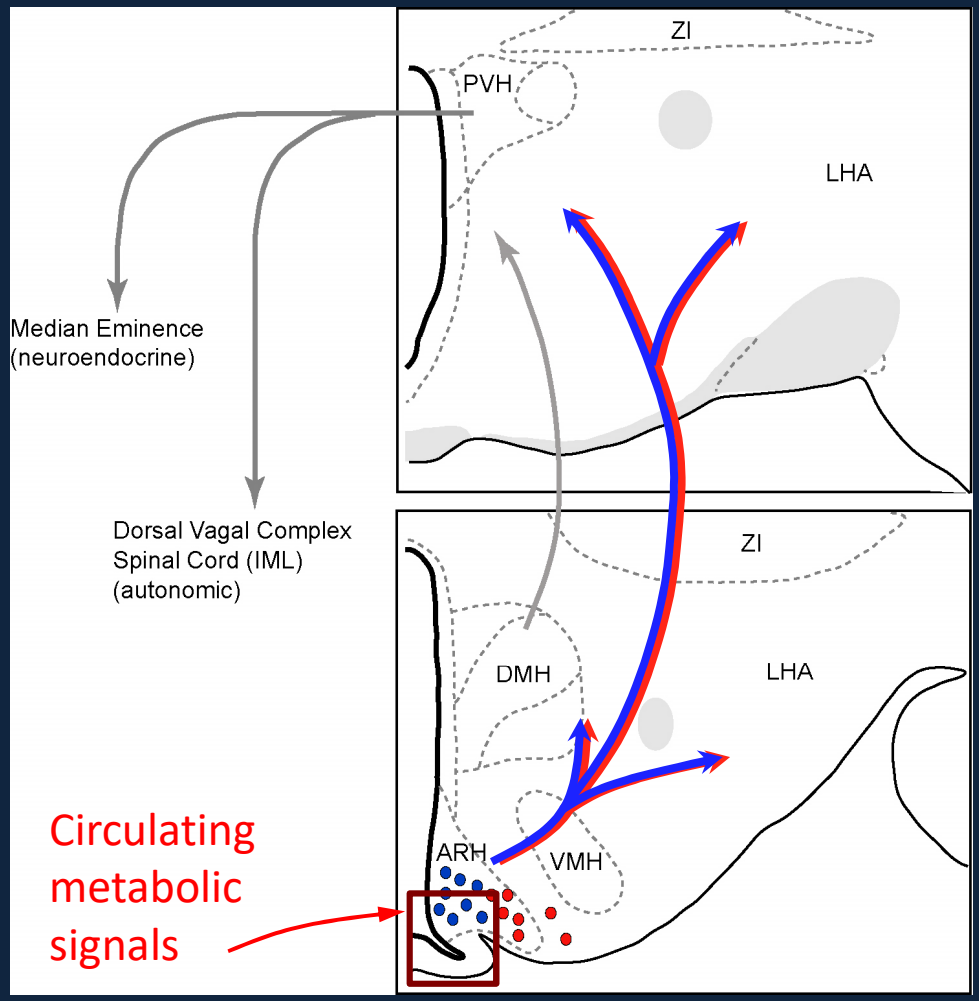

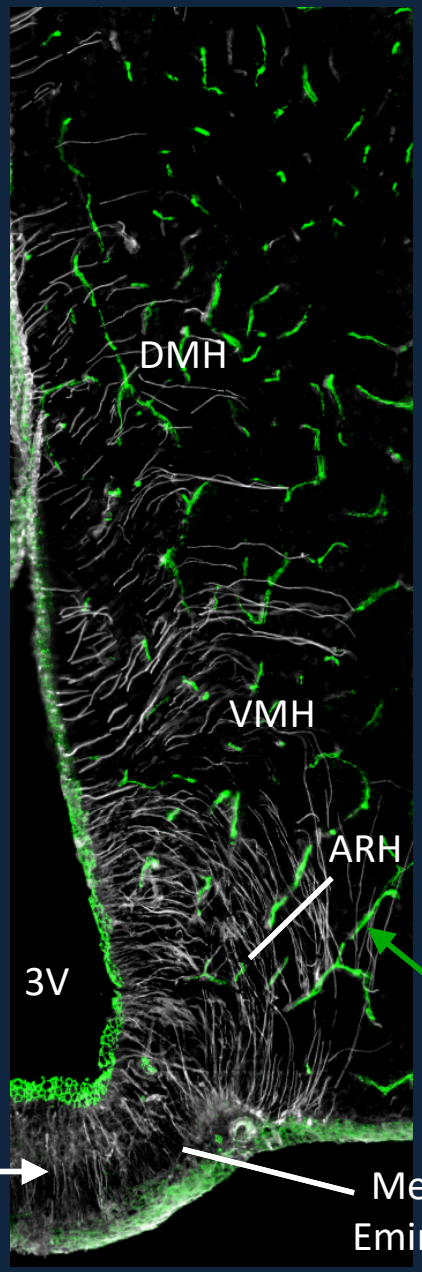

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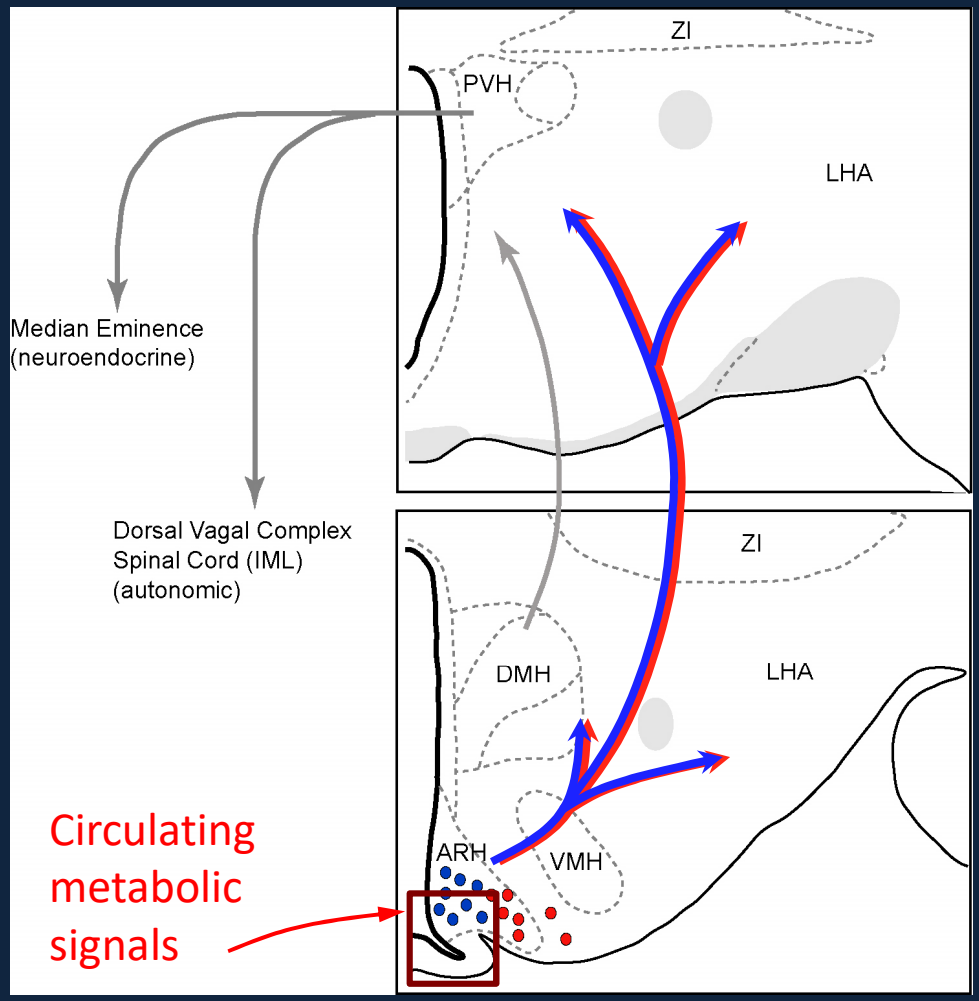

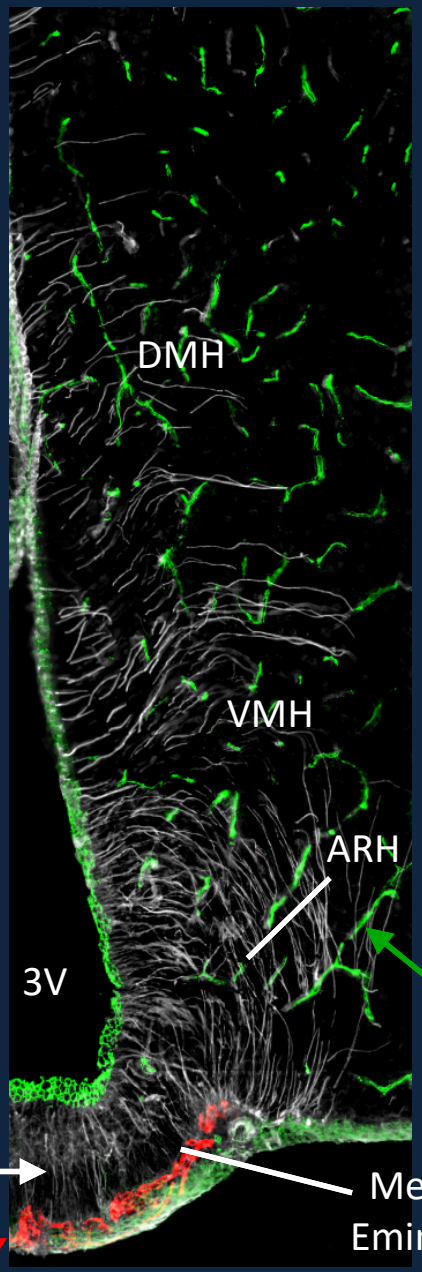

Langlet et al., Cell Metab, 17:607-617, 2013

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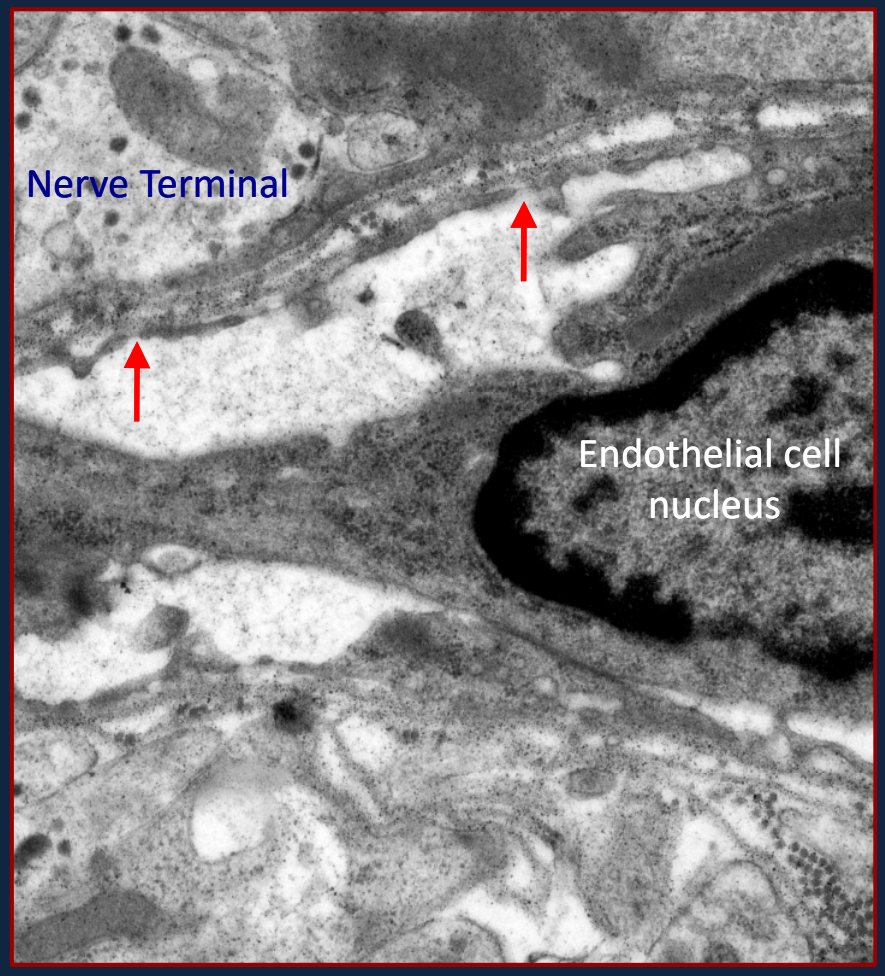

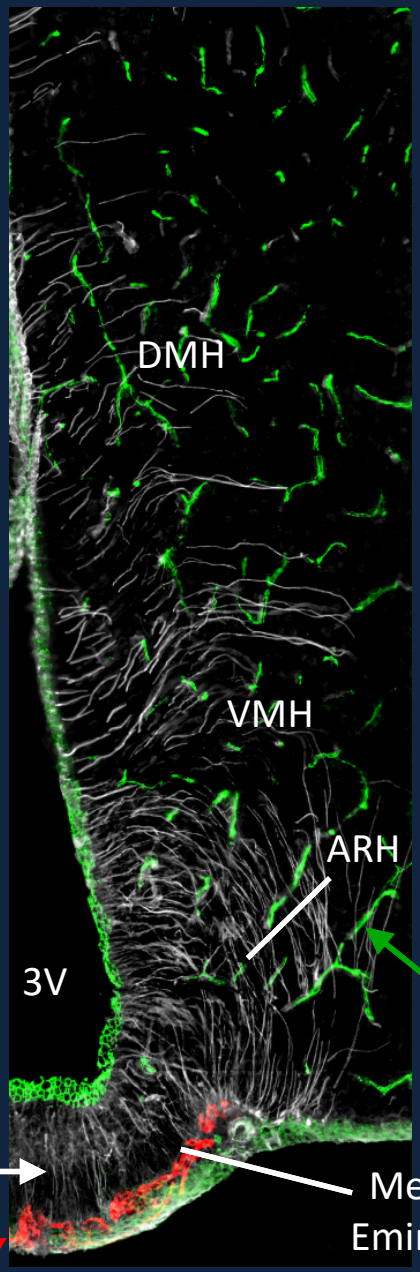

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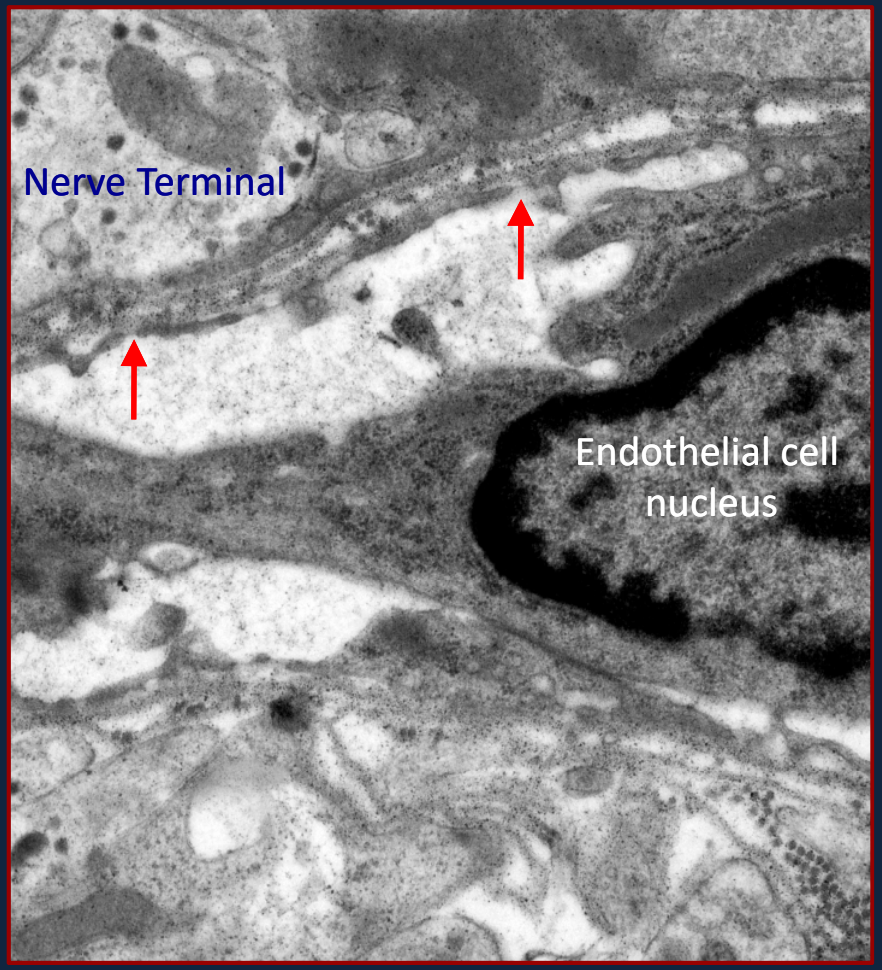
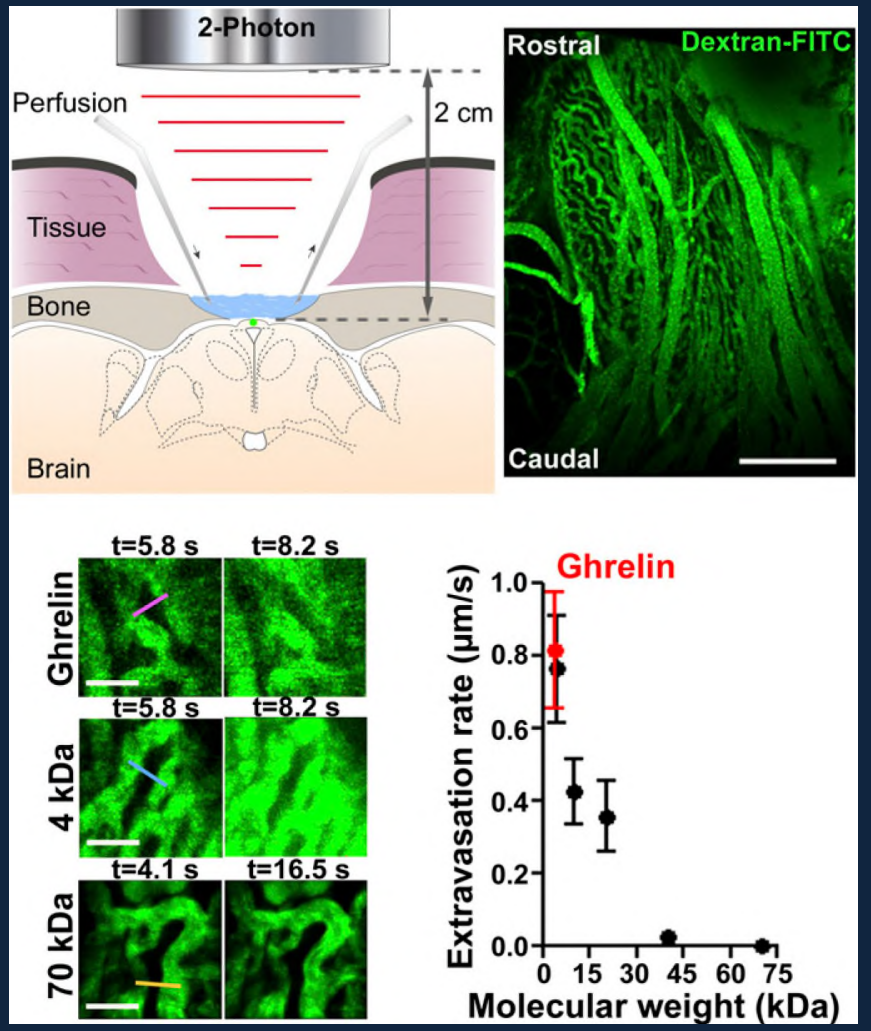
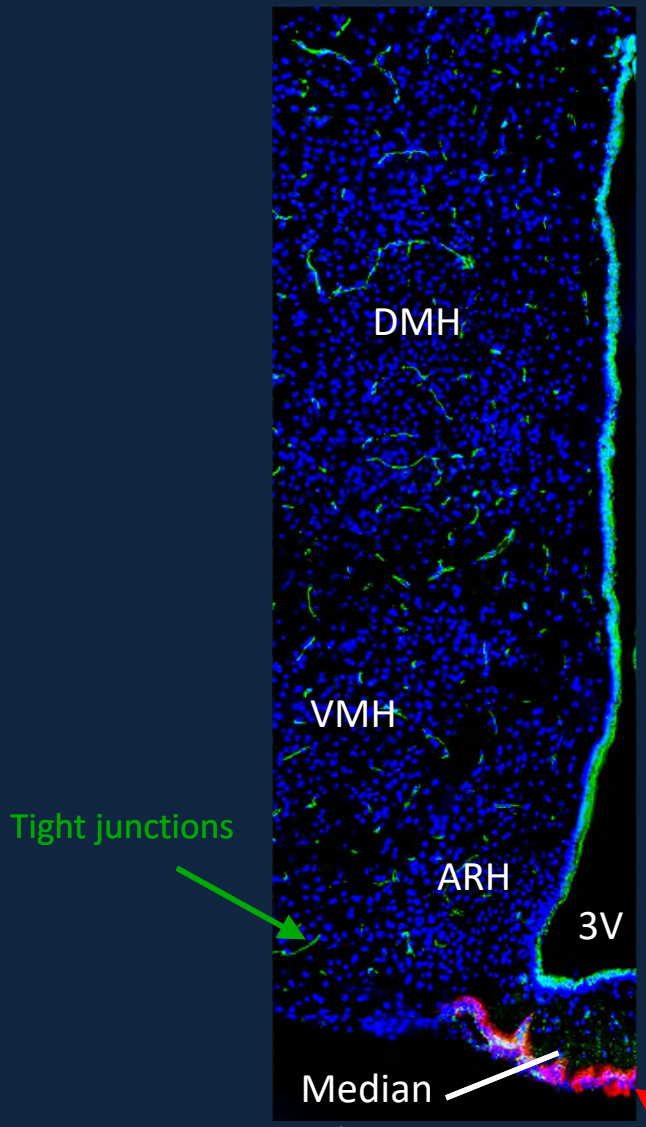
Median eminence fenestrated capillaries are permeable to circulating metabolic signals





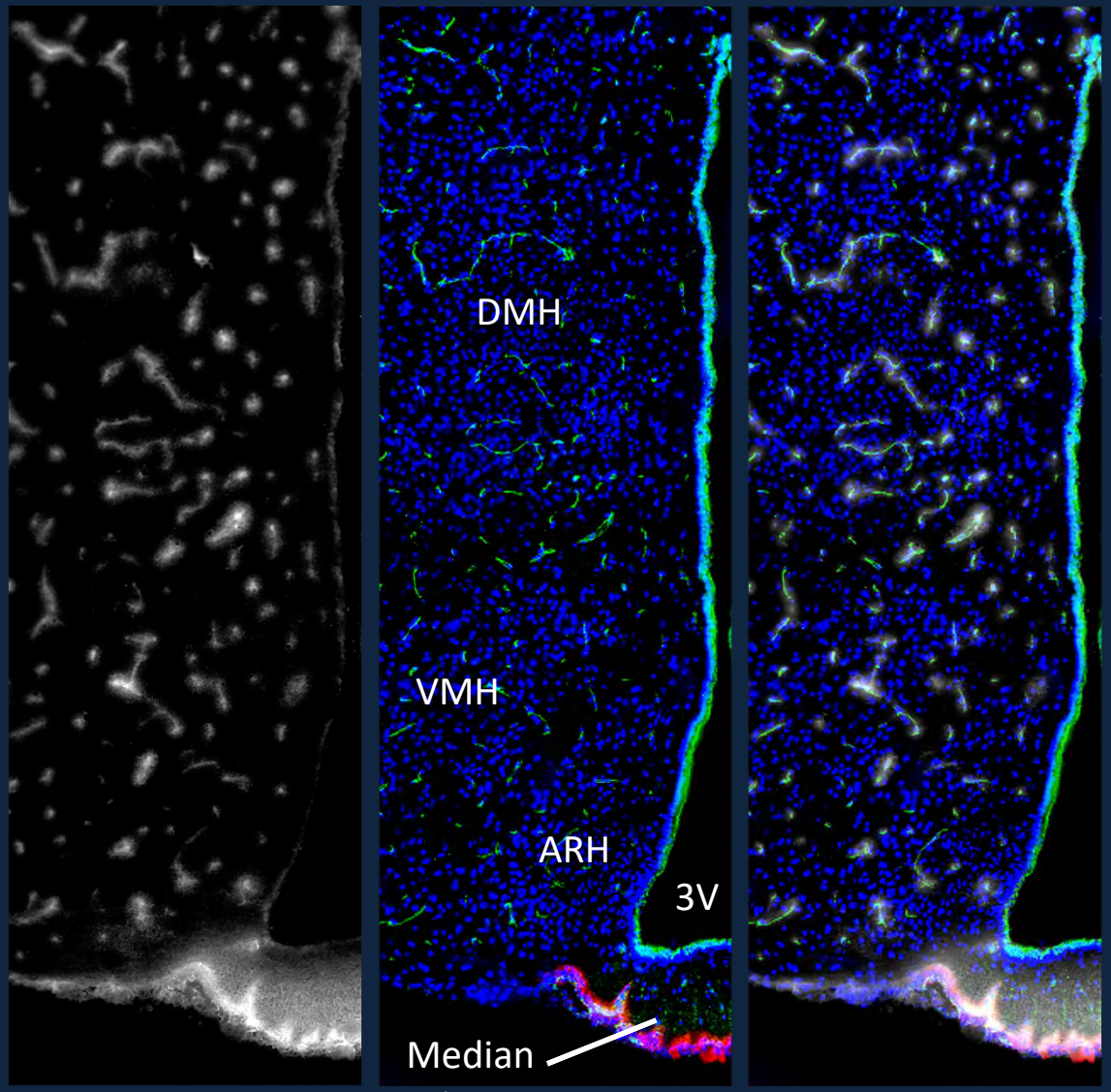
Schaeffer et al, PNAS 110: 1512-1517, 2013

Median eminence fenestrated capillaries are permeable to circulating metabolic signals, however, …



Intravenous infusion of an inert dye e.g., Evans blue (1 kDa)

Median eminence fenestrated capillaries are permeable to circulating metabolic signals, however, their diffusion appears to be restricted to the median eminence



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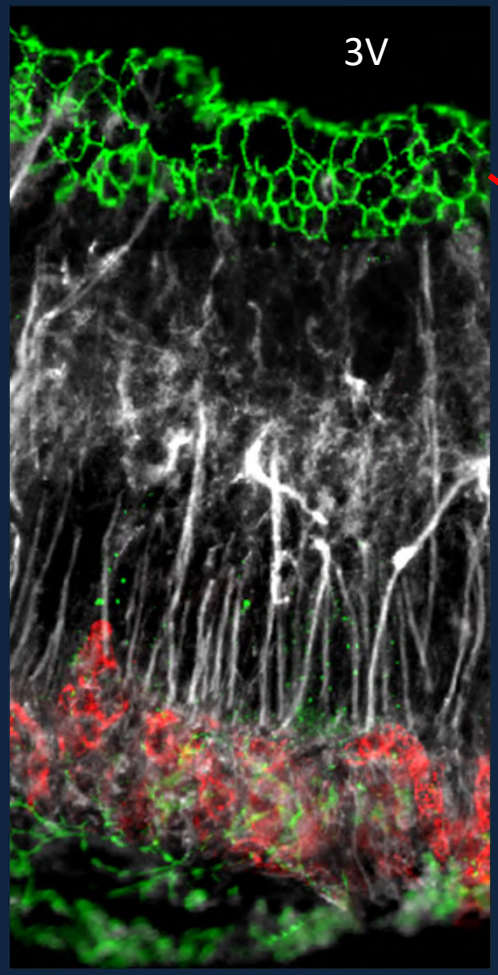
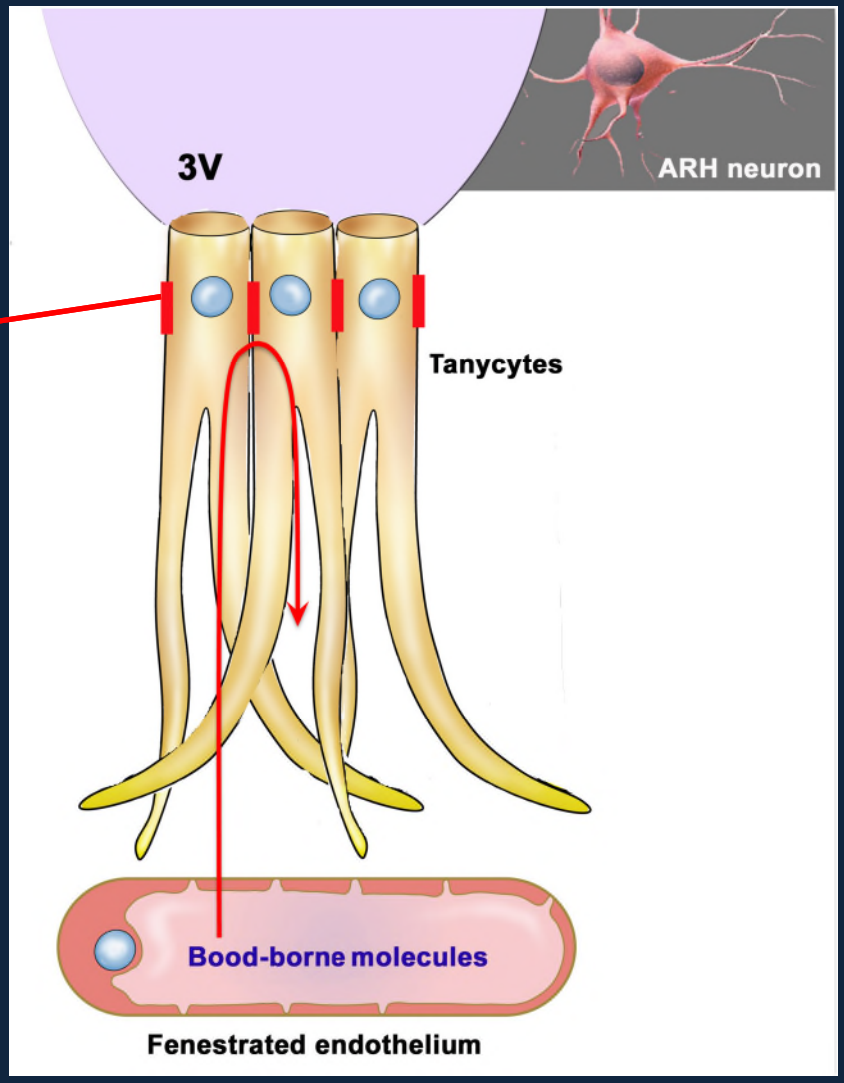
Mullier et al, J Comp Neurol 518:943, 2010

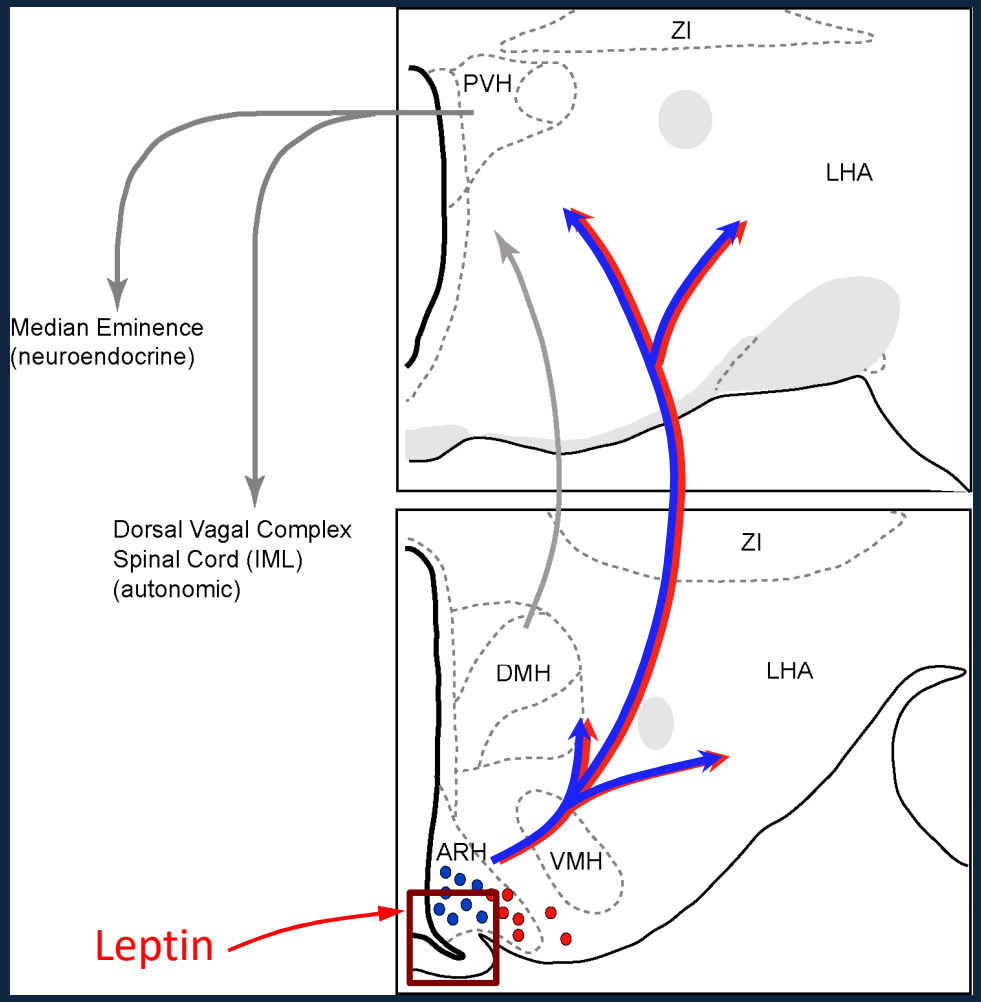
Do tanycytes gate the access of circulating metabolic signals into the brain?

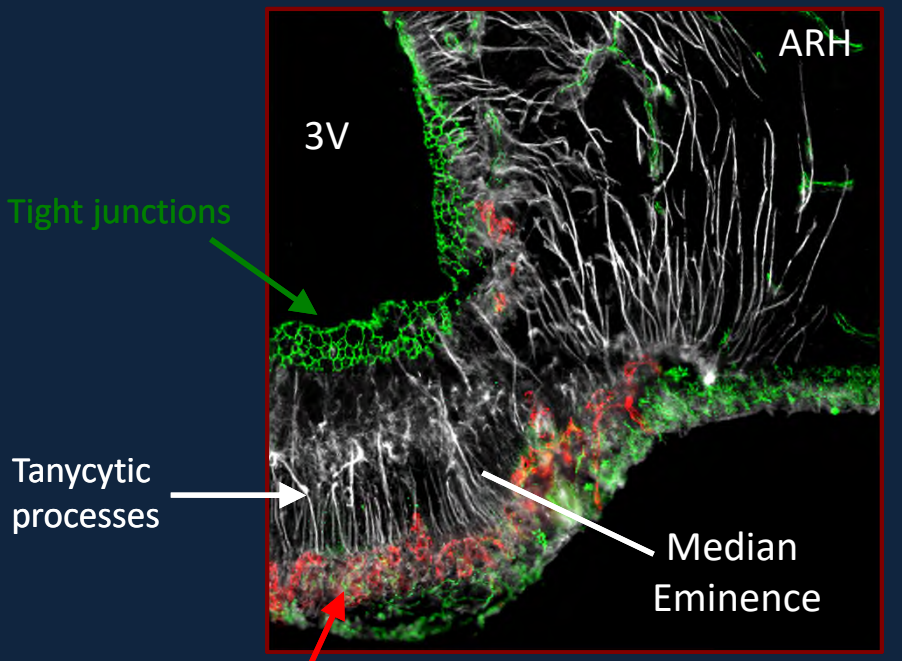


Tight junctions

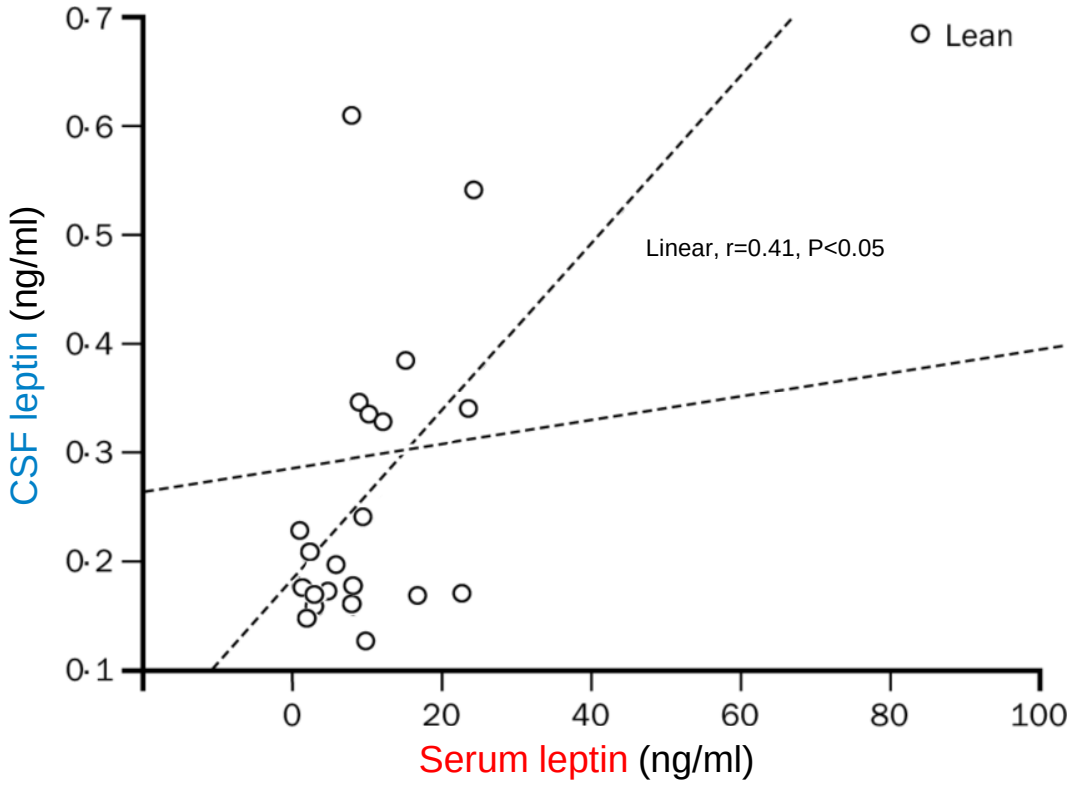


How does Leptin Enter the Metabolic Brain?



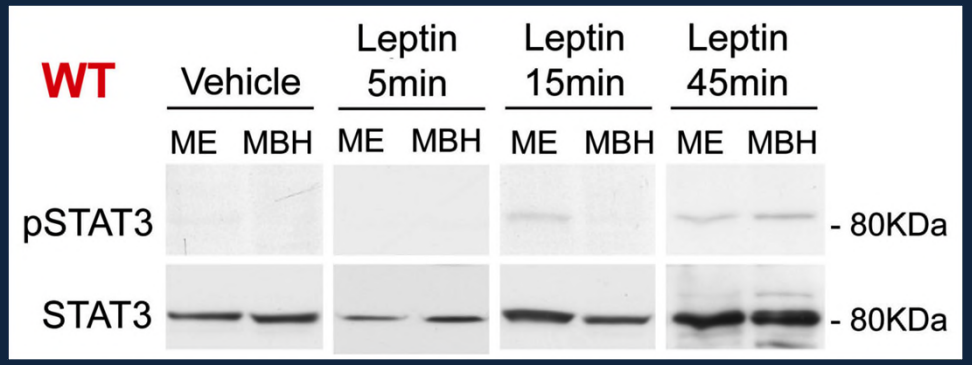


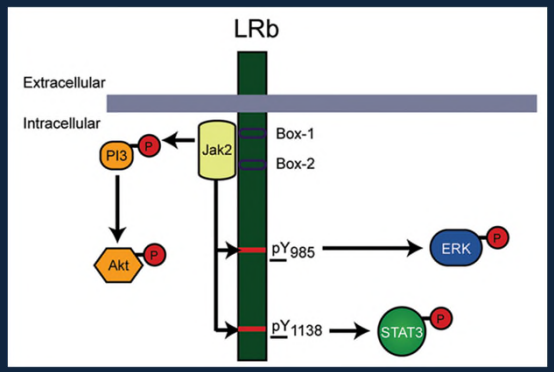
Serum and CSF leptin concentration are positively associated in lean but not obese human subjects

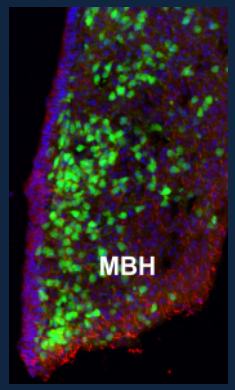


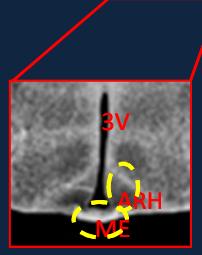
Caro et al., Lancet 348:159-161, 1996

Peripherally Administered Leptin Sequentially Activates pSTAT3 in Median Eminence Followed by MBH.









Balland et al., Cell Metab, 19, 293-301, 2014

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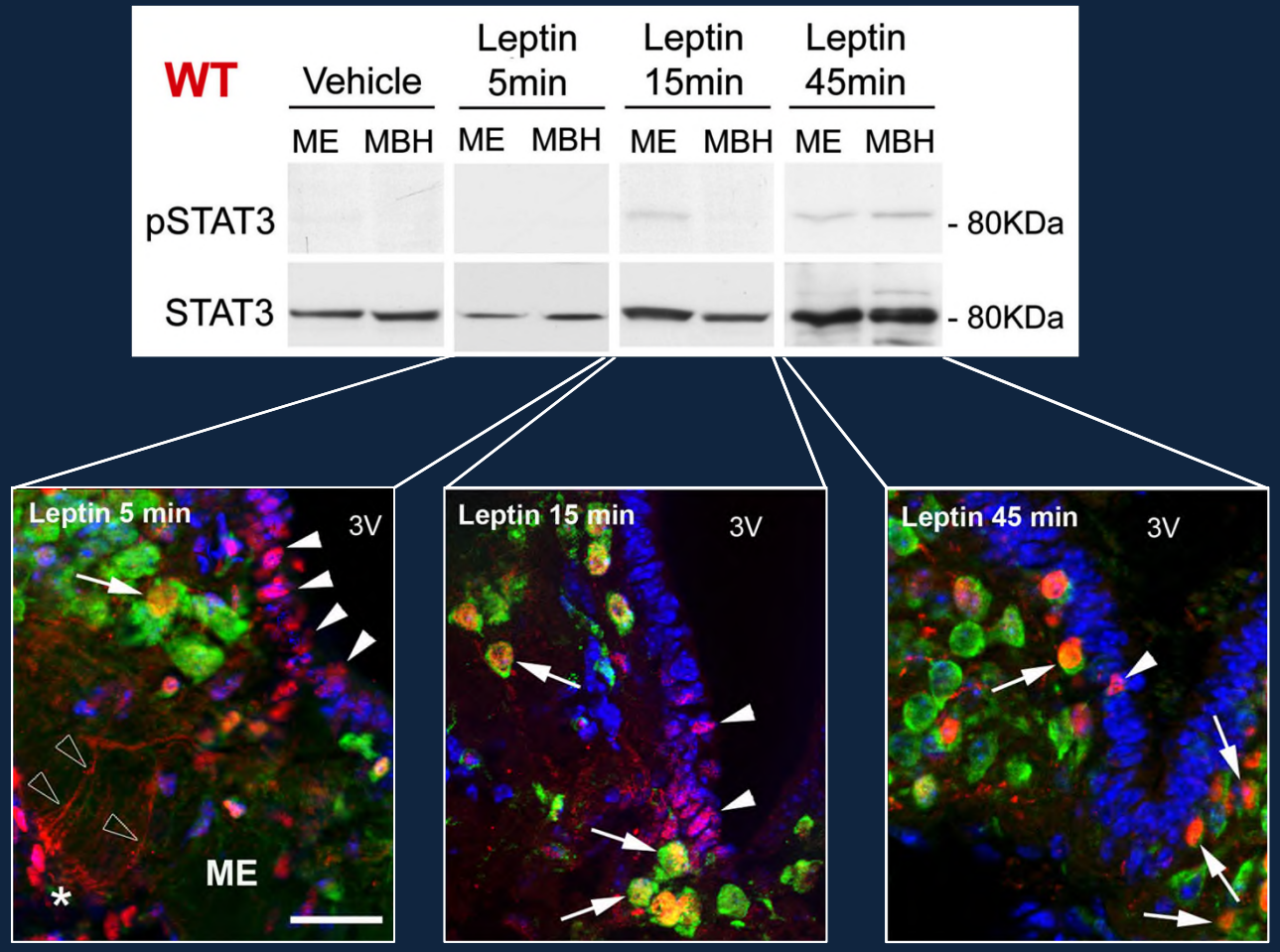
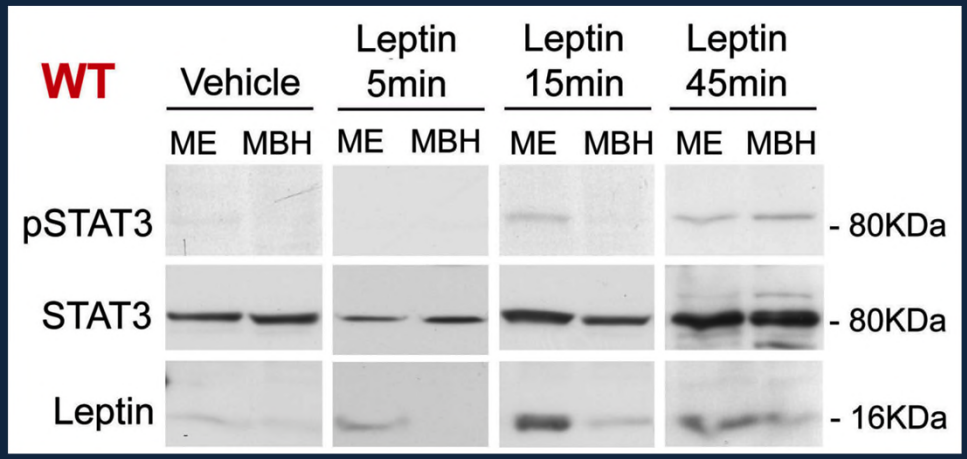


pSTAT3, HuC/D, Hoescht

Balland et al., Cell Metab, 19, 293-301, 2014

Exogenous Leptin is Detectable Only in the Median Eminence at 5 min but progressively invades the MBH at 15 and 45 min



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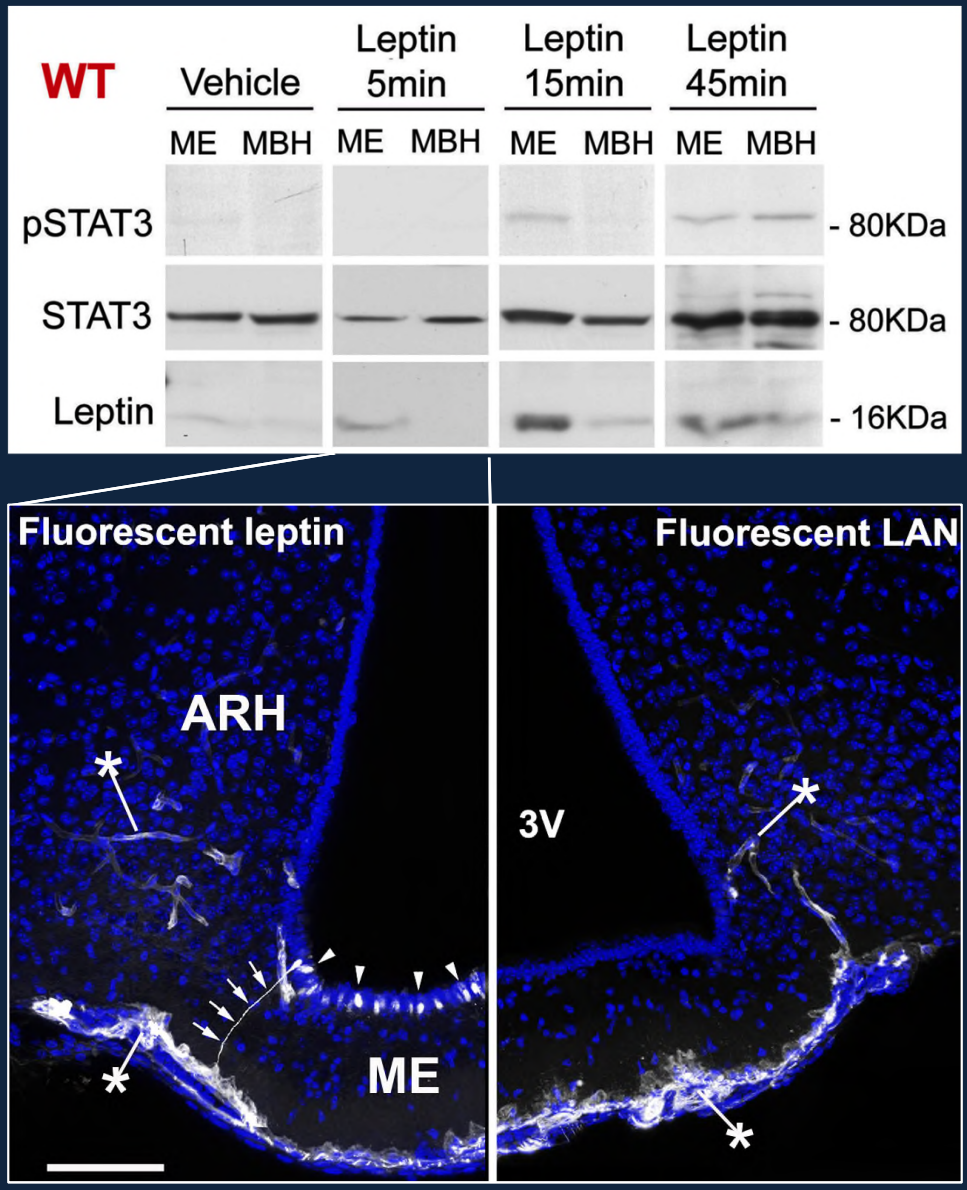
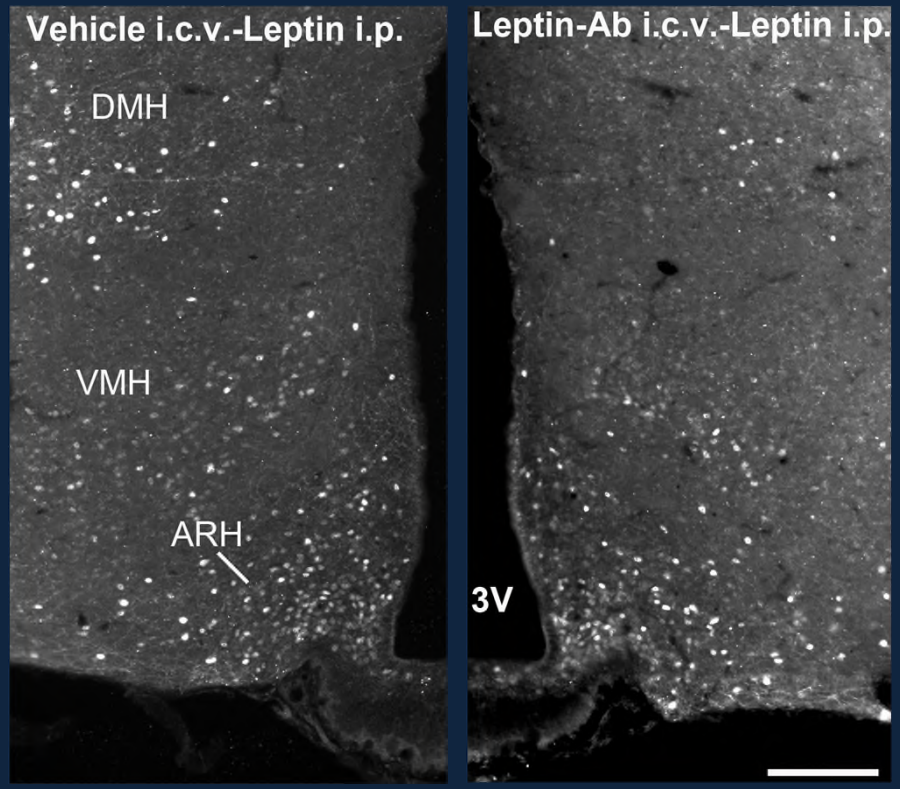
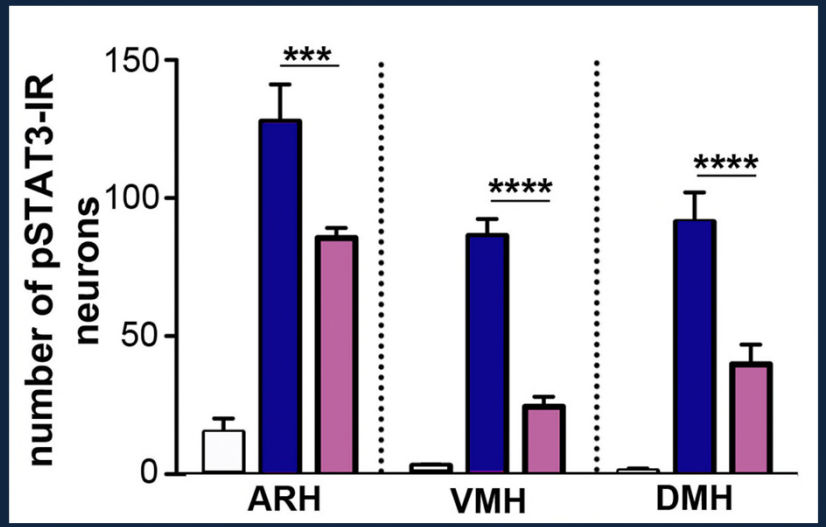


LAN: leptin with an inactivating point mutation

Balland et al., Cell Metab, 19, 293-301, 2014

The access of blood-borne leptin ti the CSF is required for STAT3 activation in neurons of the mediobasal hypothalamus





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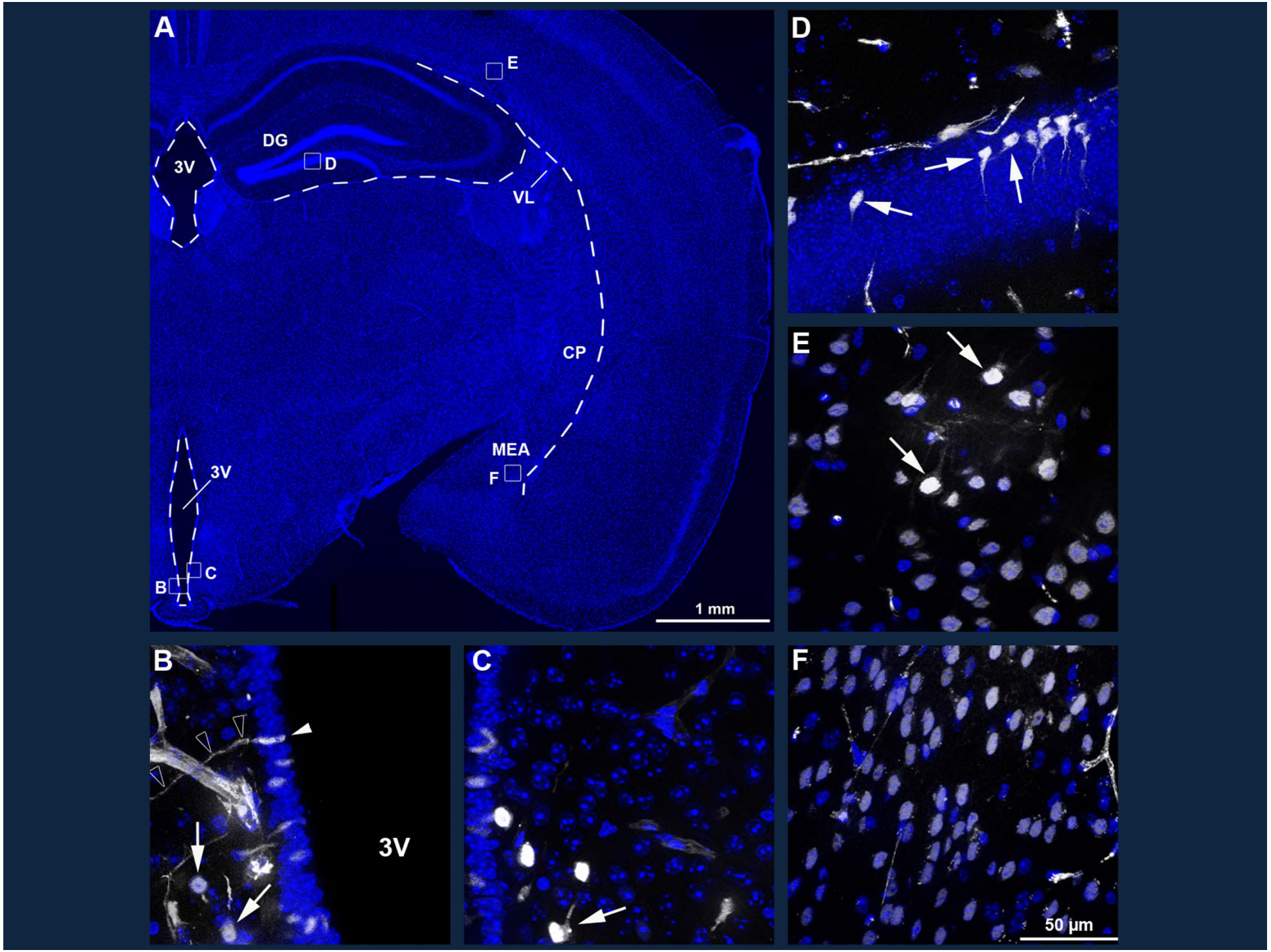
A
E
DG
D
3V
VL
CP
MEA
F
3V
C
B
1 mm
D
E
B
3V
C
F
50 µm

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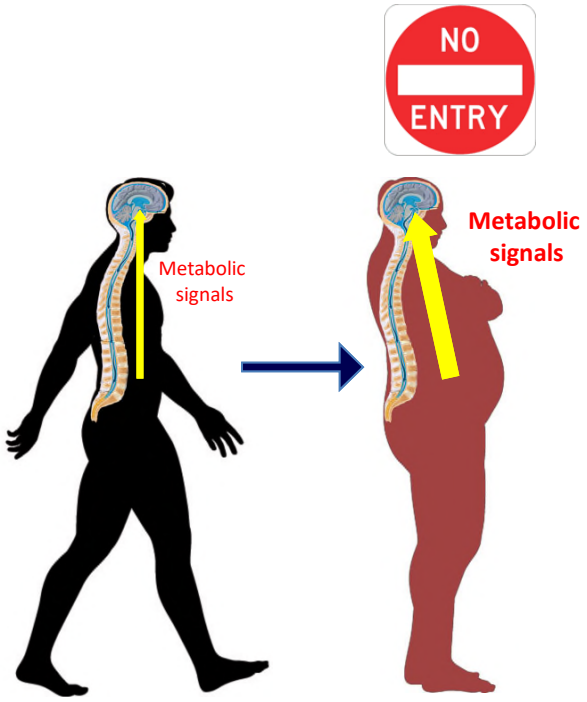

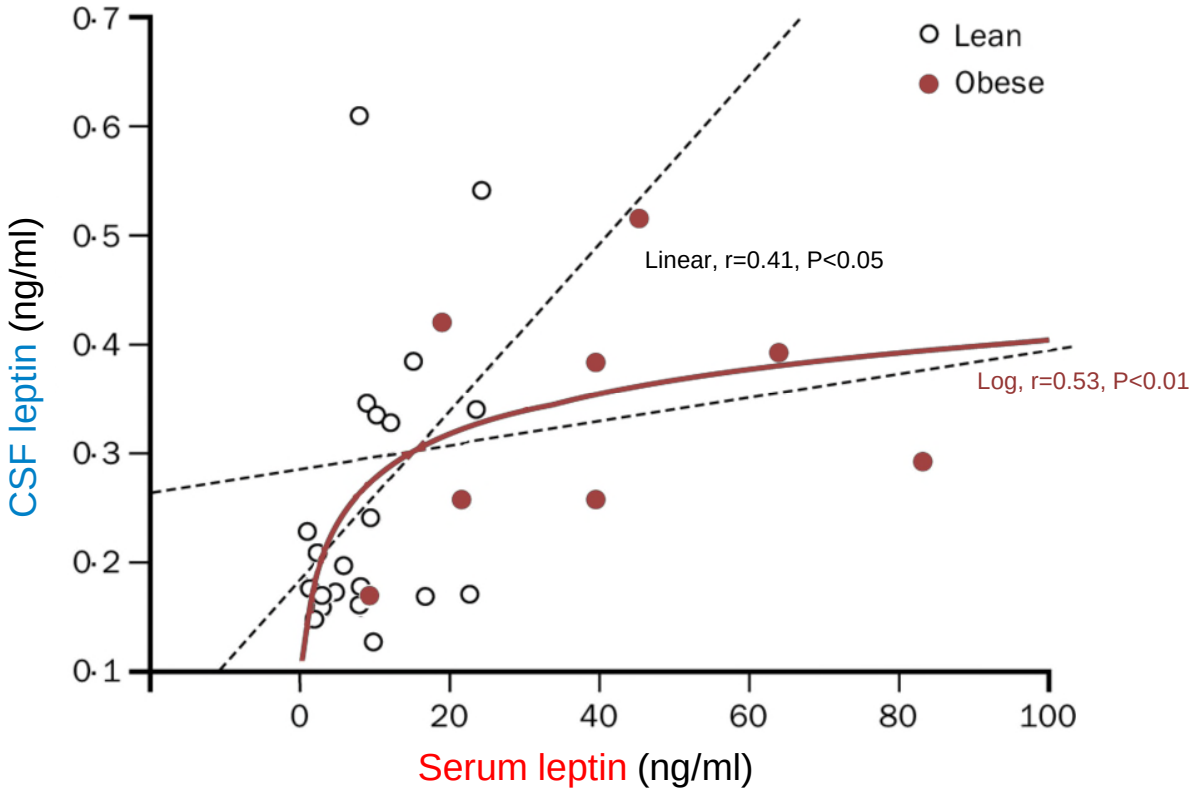

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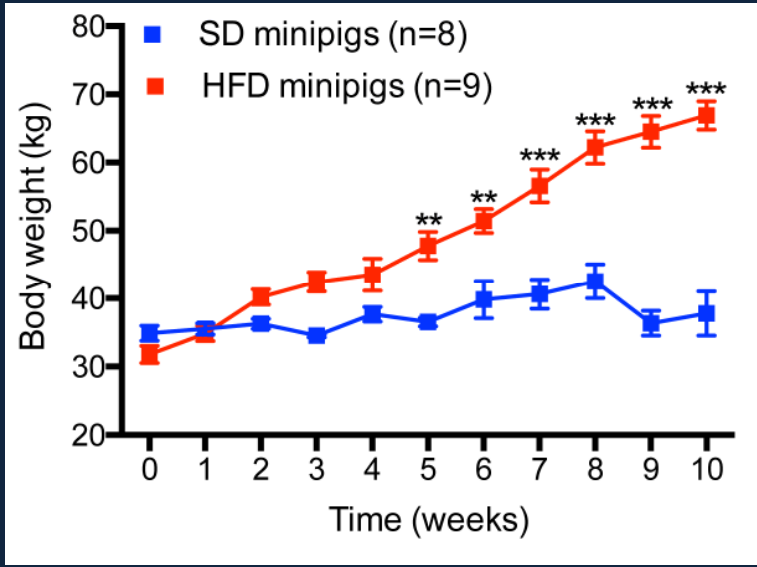
Kinetics of the alteration of the transport of leptin across the blood-CSF barrier in diet-induced obesity?



Chmielewski et al in preparation

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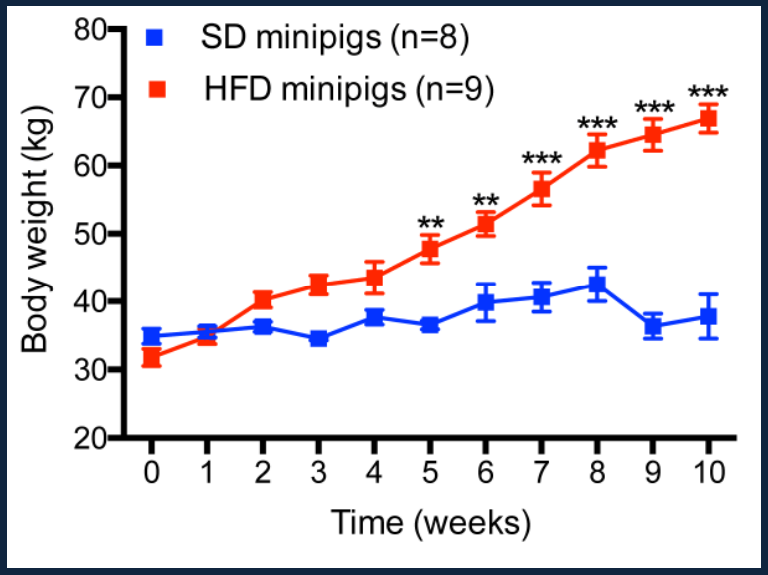
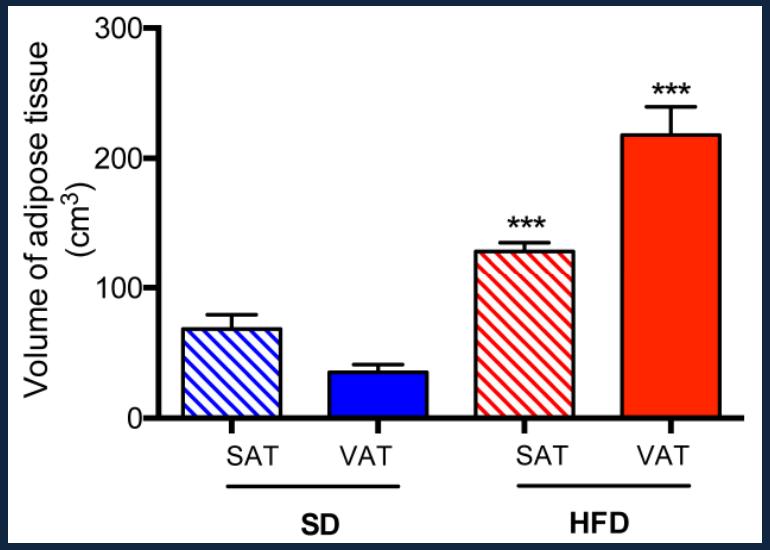
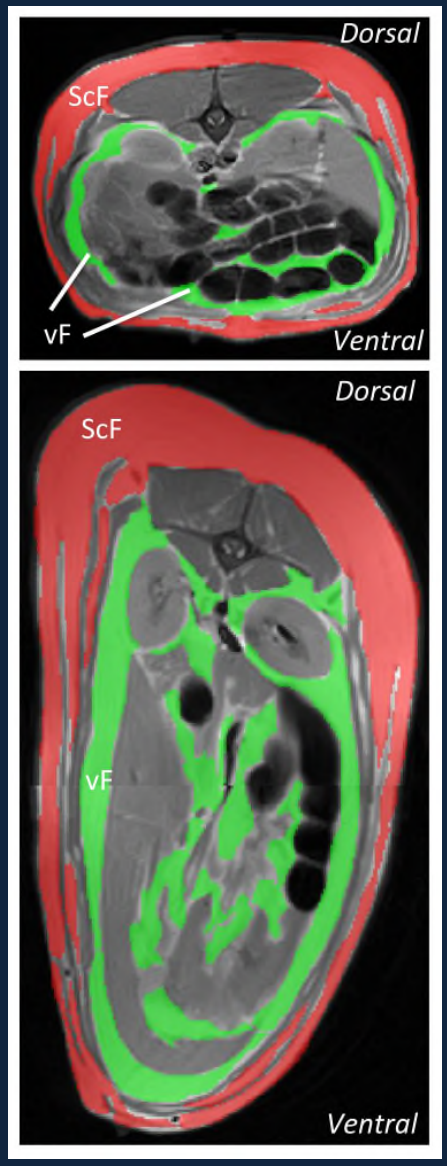
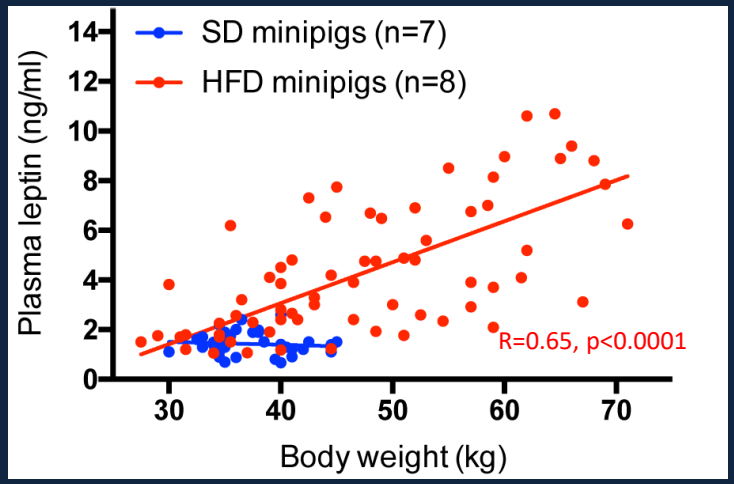






Chmielewski et al in preparation

Plasma leptin is positively associated with body weight in minipigs fed on a high fat diet (HFD)



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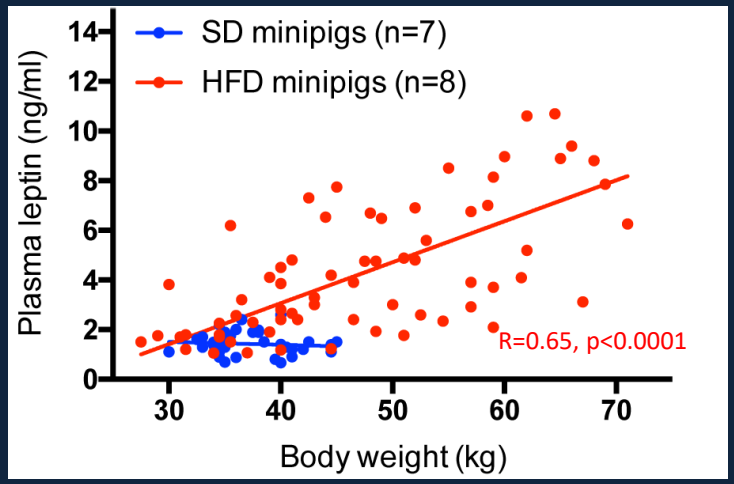

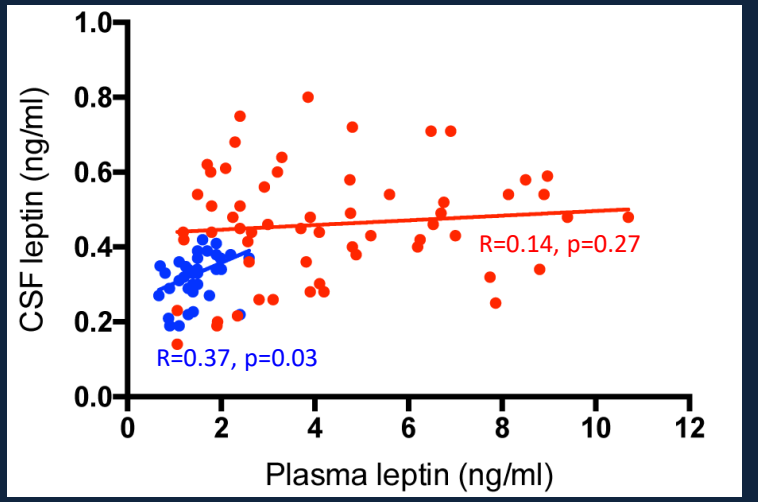

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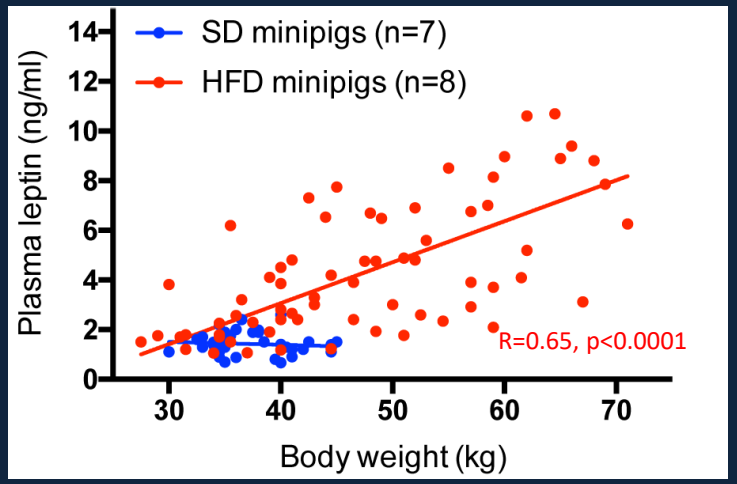
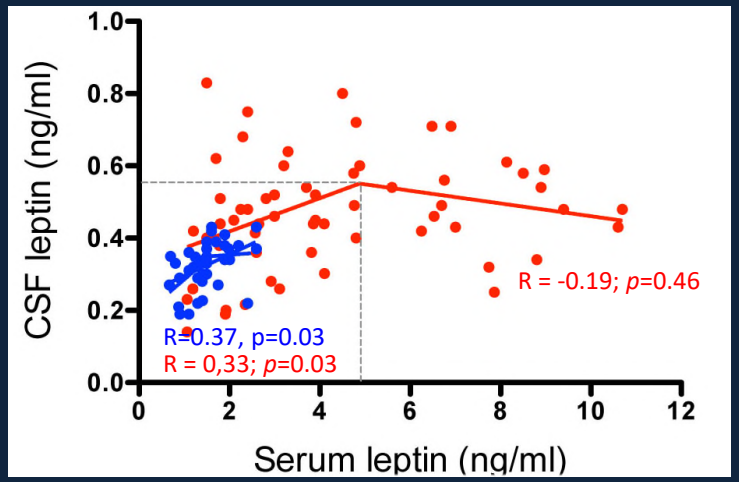
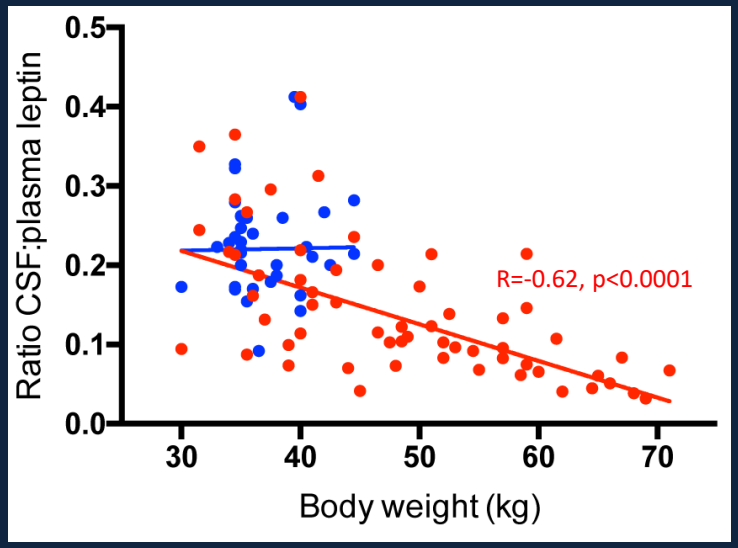
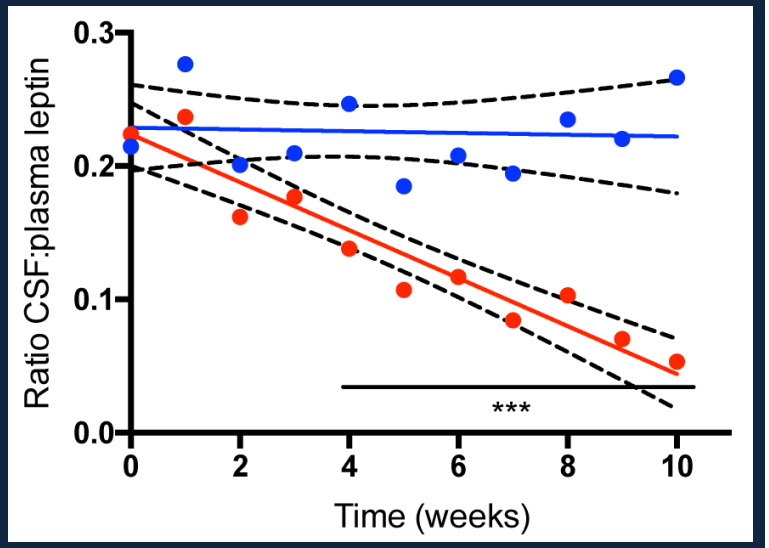




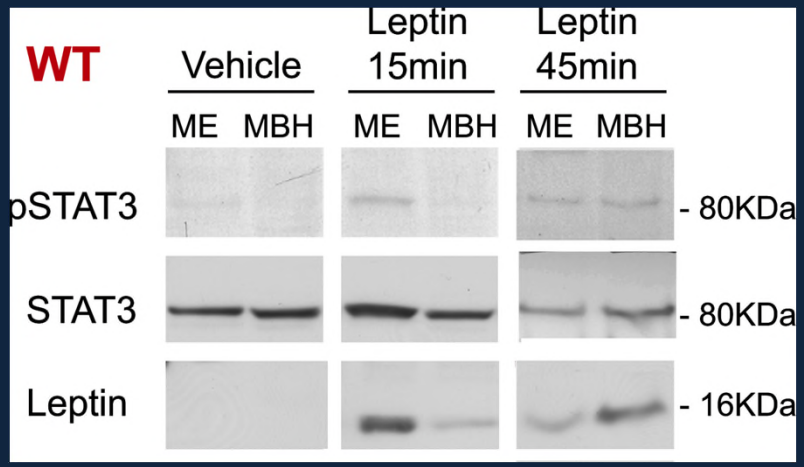


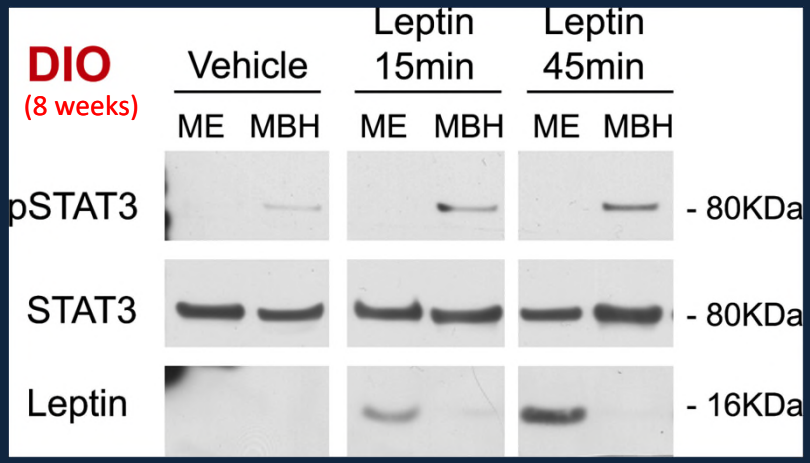


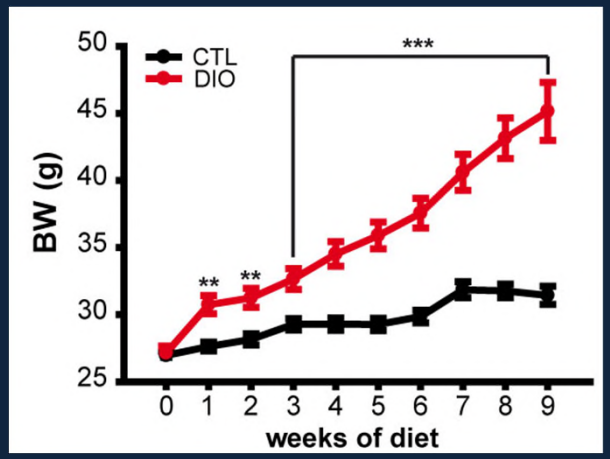
Chmielewski et al in preparation

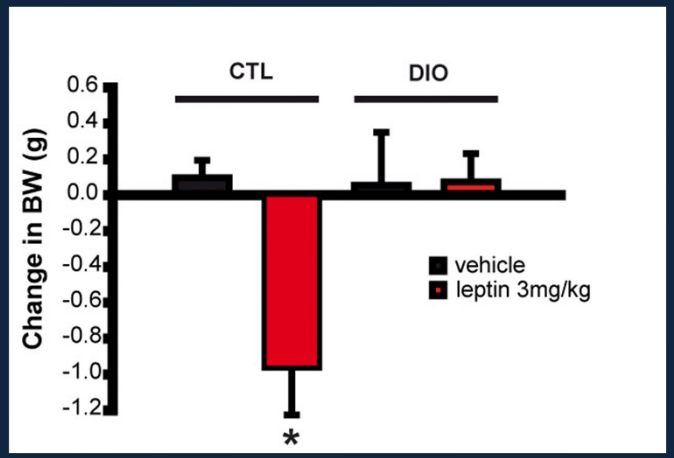
Is tanycyte-mediated leptin transport into the brain altered in diet-induced obese mice?

Leptin Transport into the Hypothalamus via the ME is Disrupted in mice with Diet-Induced Obesity (DIO)



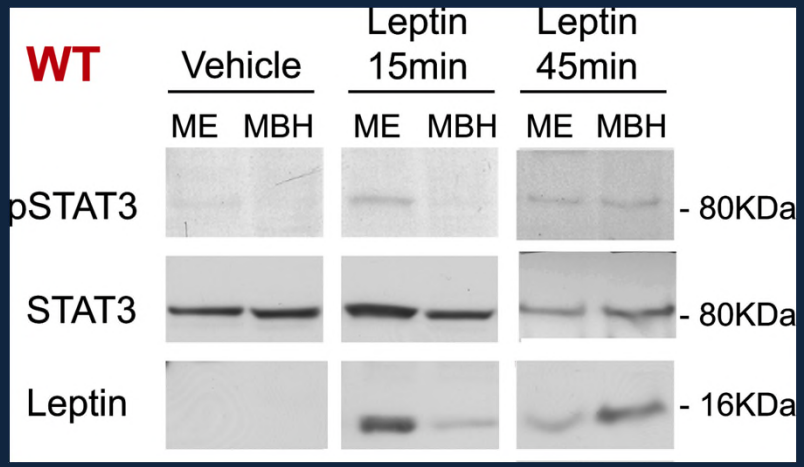


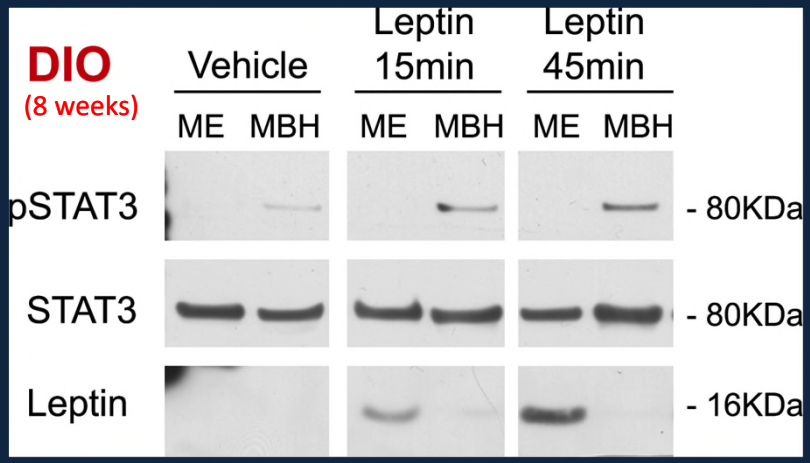


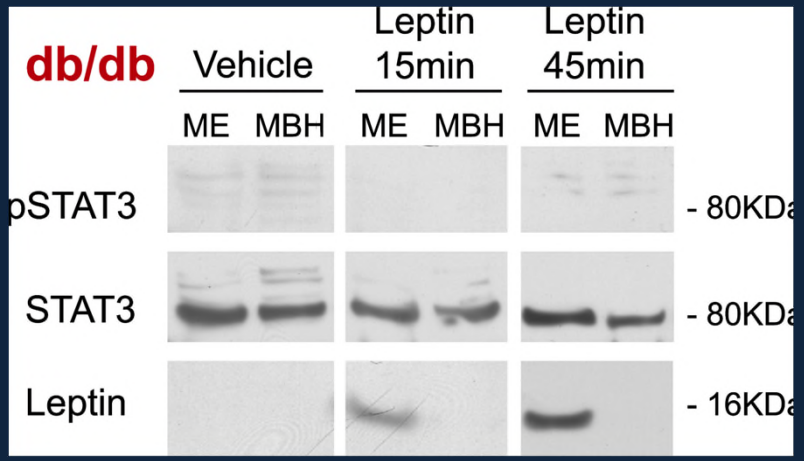


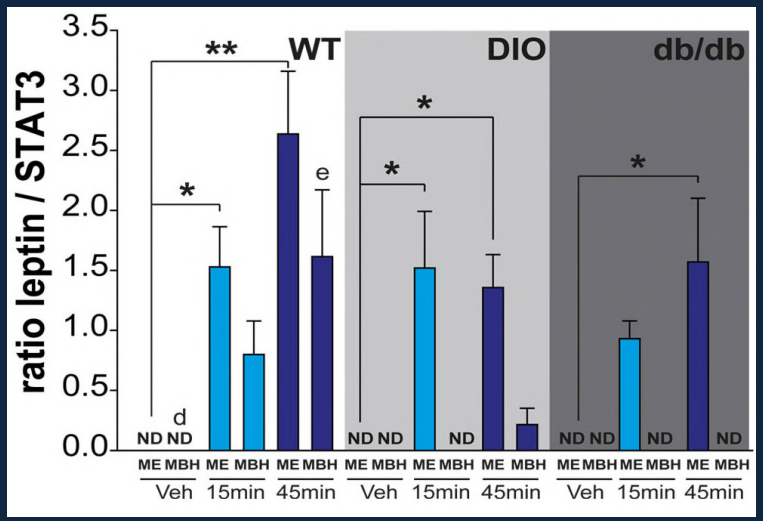
Balland et al., Cell Metab, 19, 293-301, 2014

Leptin Transport into the Hypothalamus via the ME requires LepR Signalling and is Disrupted in Animals with Diet-Induced Obesity (DIO)









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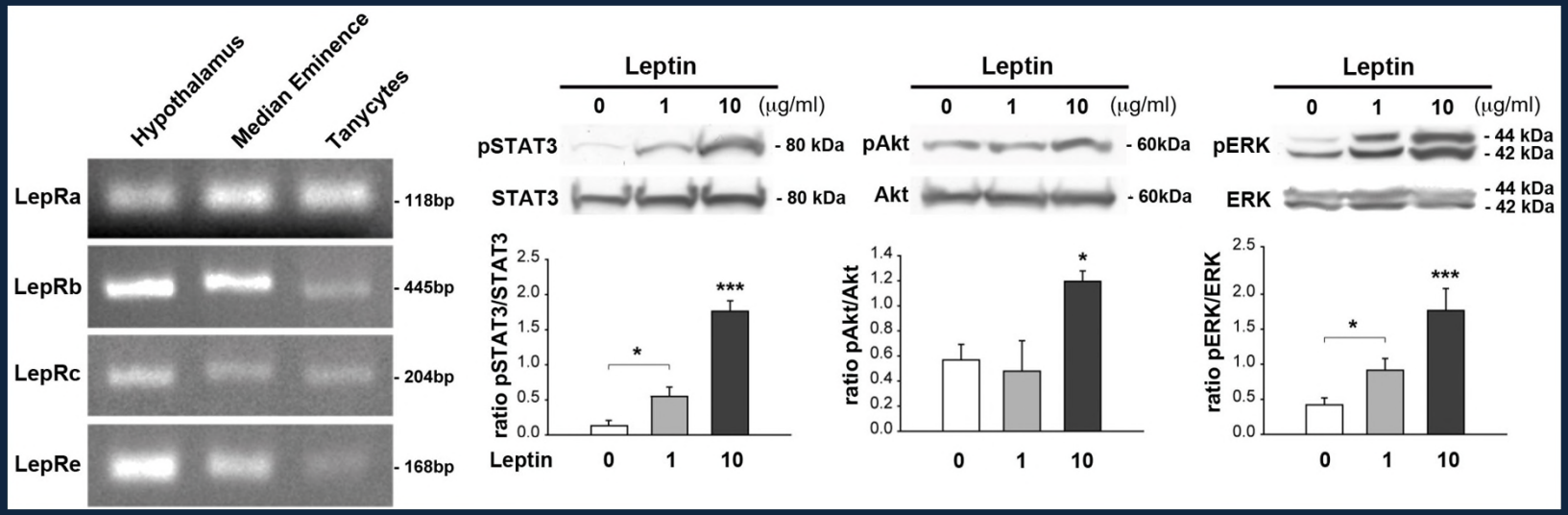
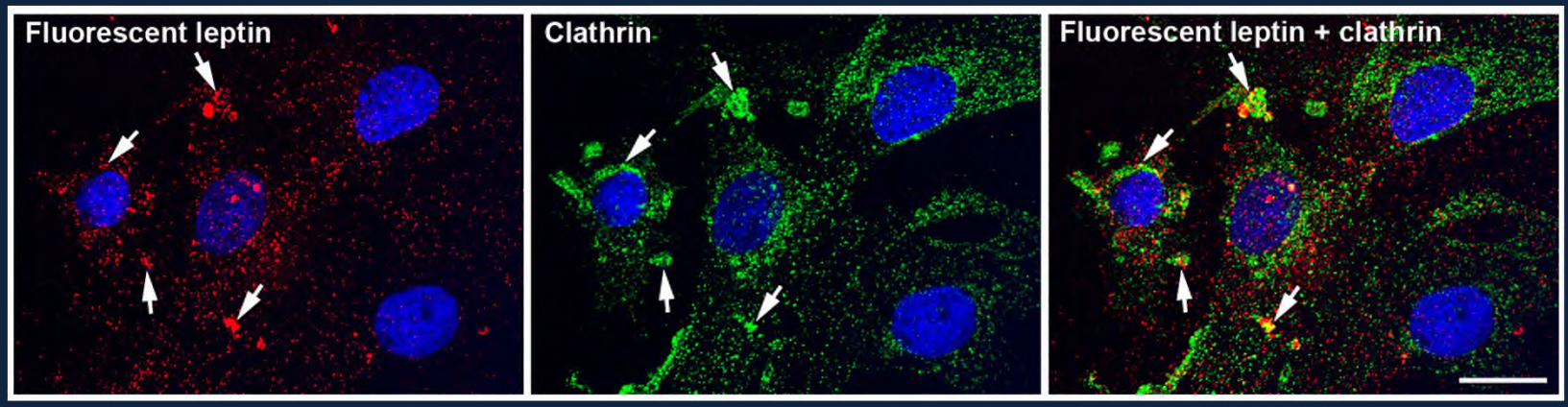
Intermediary Conclusion

The hypothalamic median eminence thus appears to be a route through which leptin enters the brain and tanycytes may act as a checkpoint along this route

Tanycytes of the Median Eminence Express Functional LepR and Internalize Leptin through Clathrin-Coated Vesicles *in vitro*





Balland et al., Cell Metab, 19, 293-301, 2014

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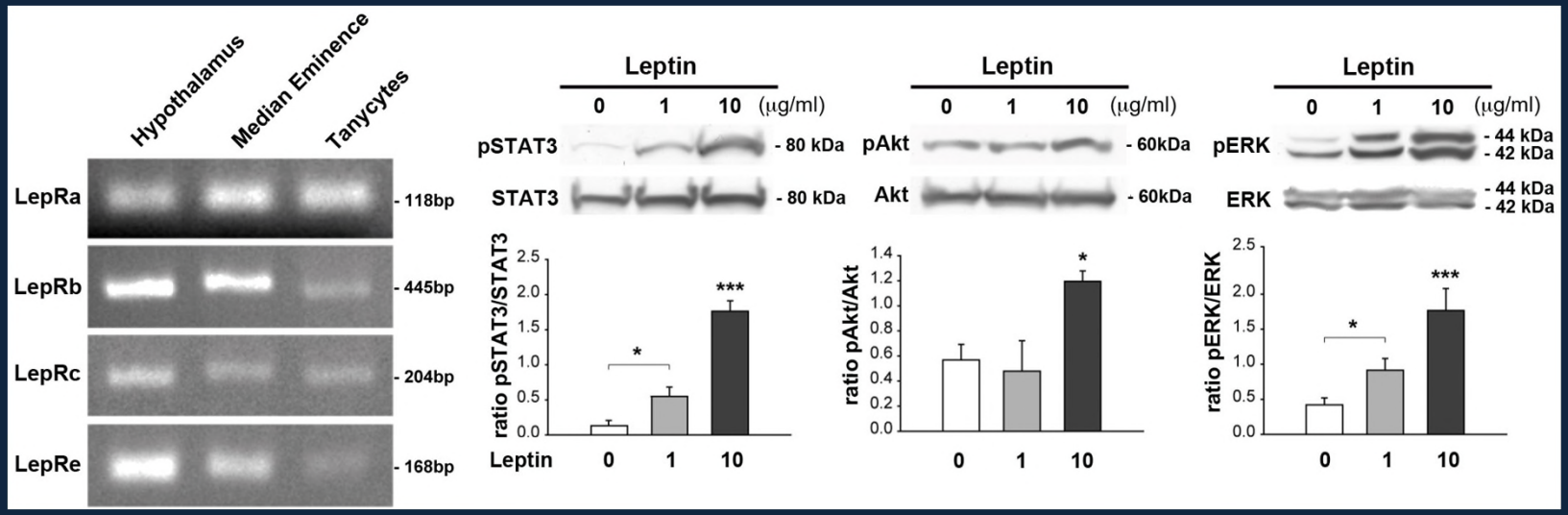
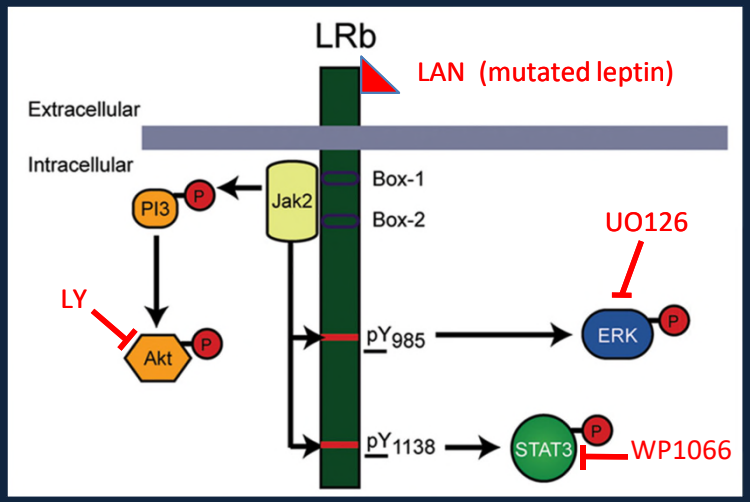
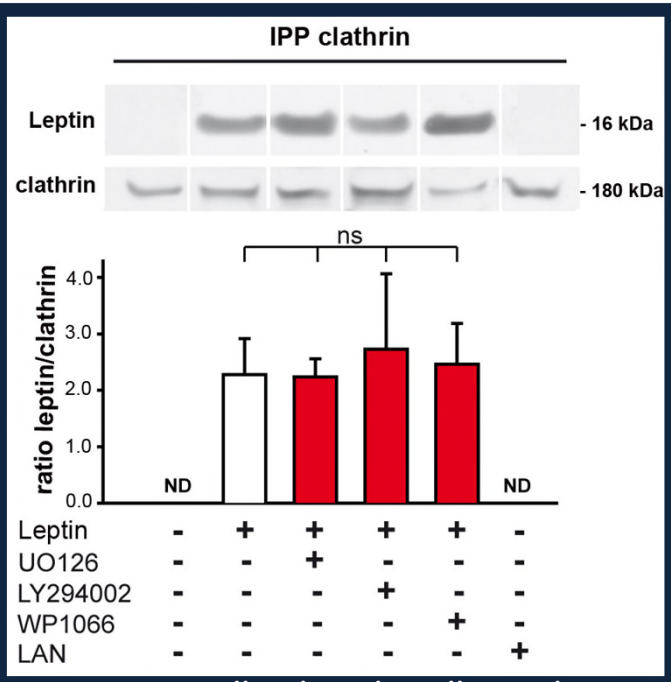
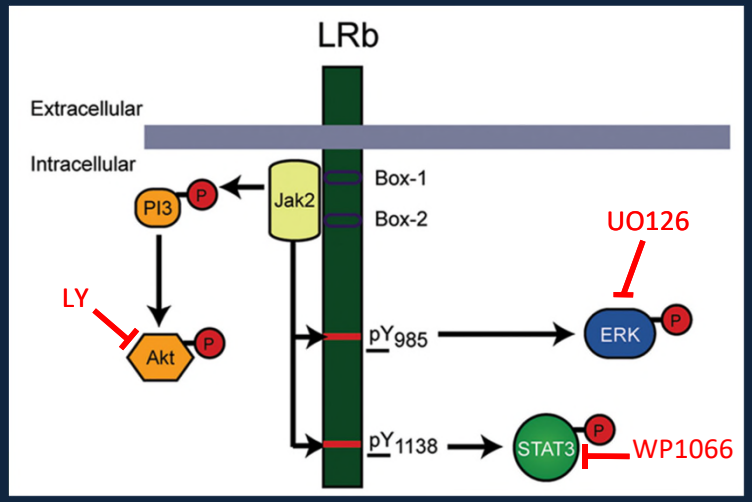




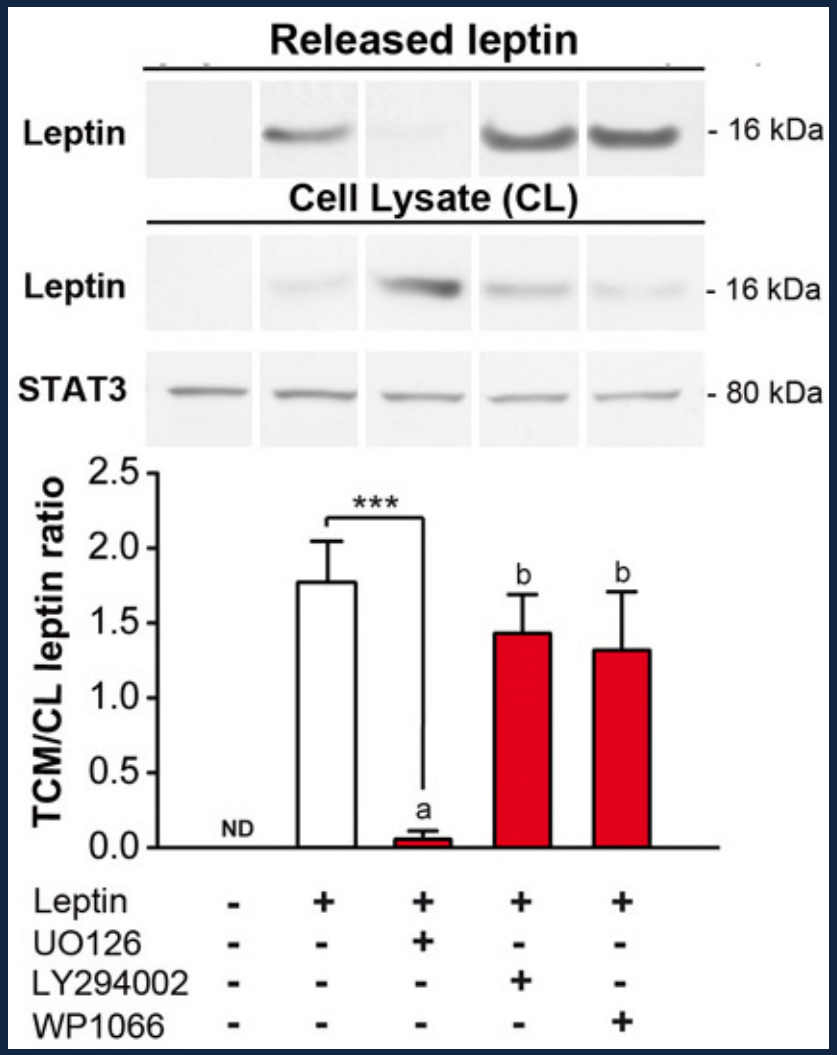


Balland et al., Cell Metab, 19, 293-301, 2014

Tanycytes of the Median Eminence Release Captured Leptin via an ERK-dependent Signalling Pathway *in vitro*



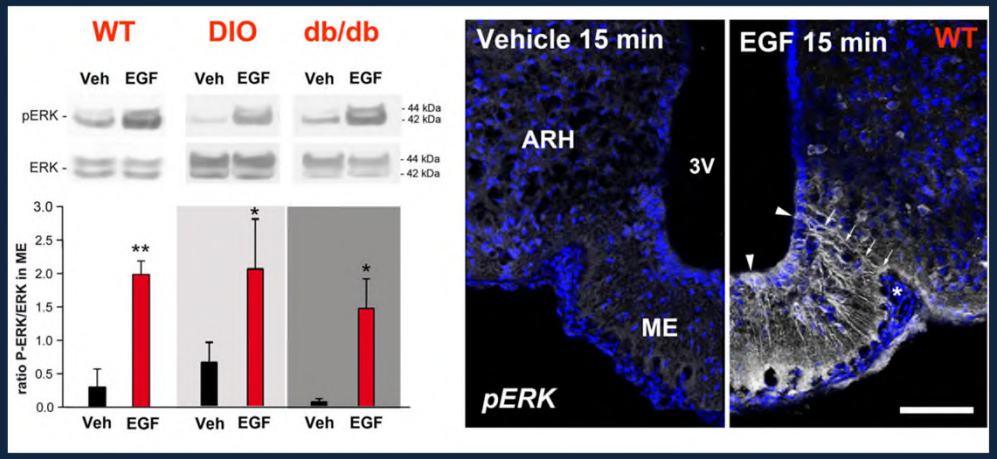
TCM: tanycyte conditioned medium



Balland et al., Cell Metab, 19, 293-301, 2014

Can defective translocation from ME to MBH in obese mice be rectified by activating ERK pathway *in vivo ?*

EGF-mediated Activation of ERK Signalling in the Median Eminence



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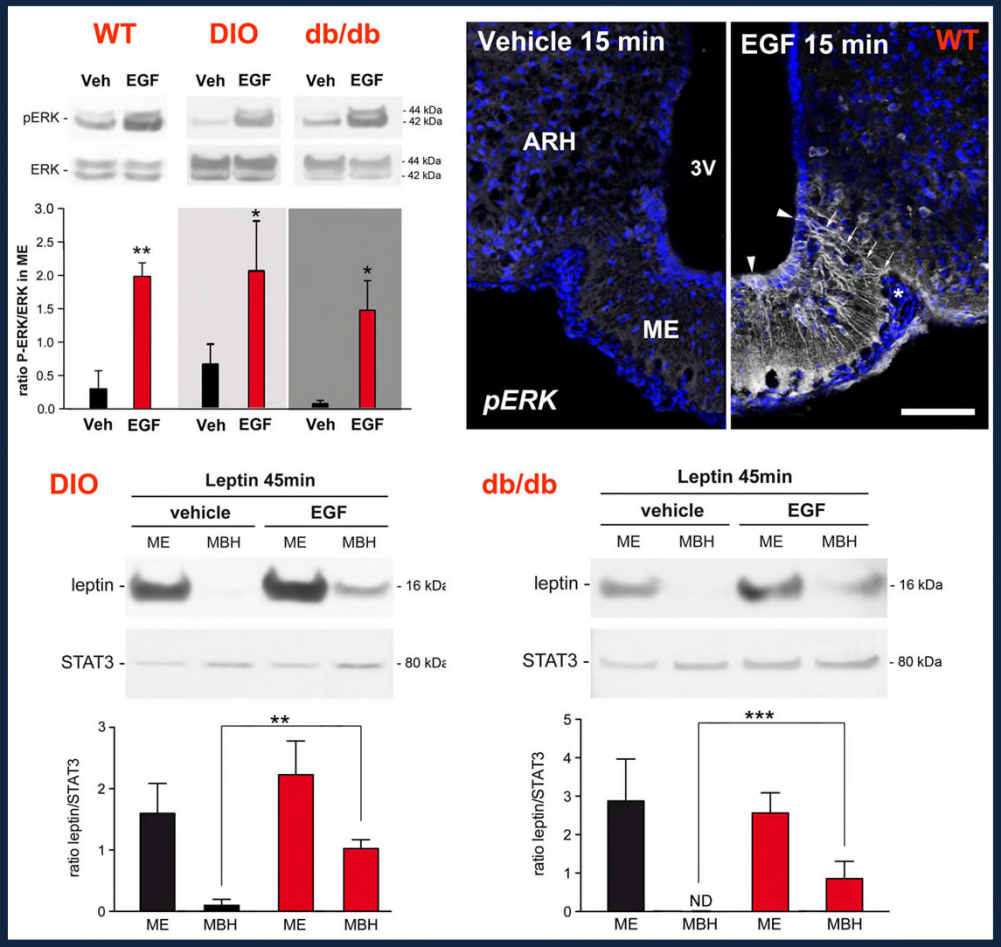
EGF-mediated Activation of ERK Signalling in the Median Eminence restores Leptin Transport into the Hypothalamus



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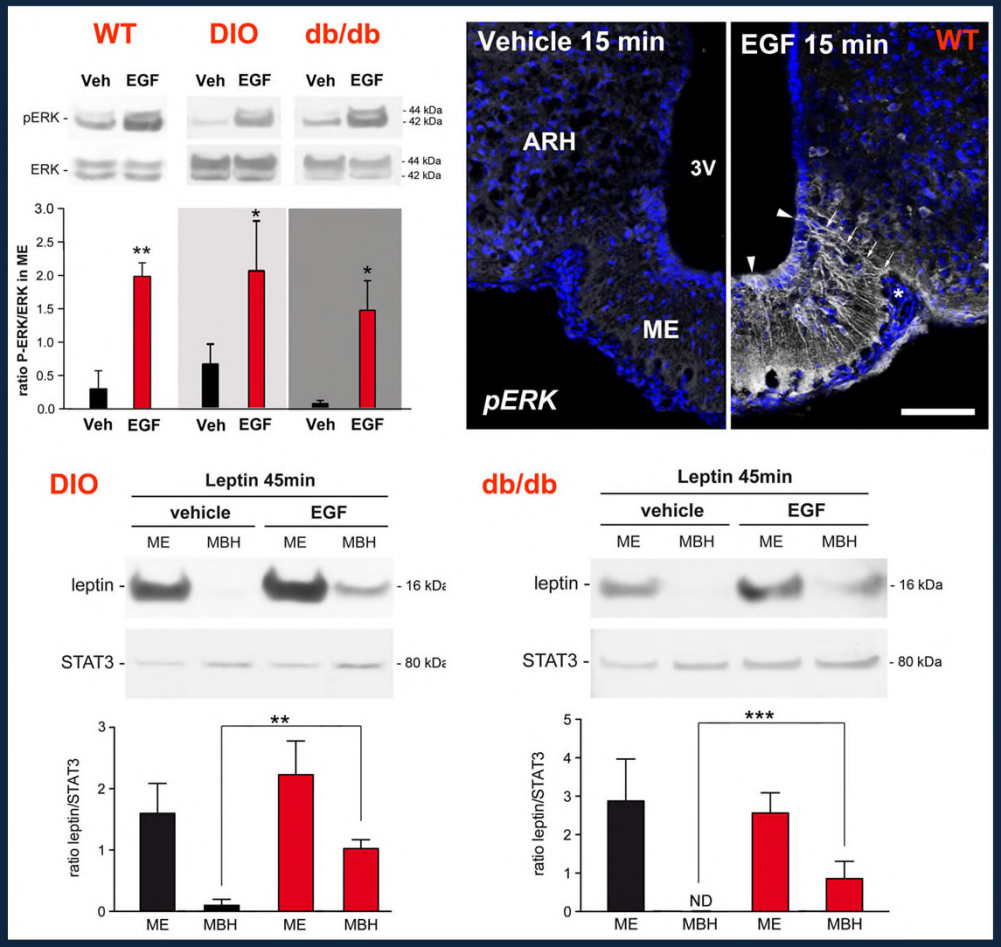
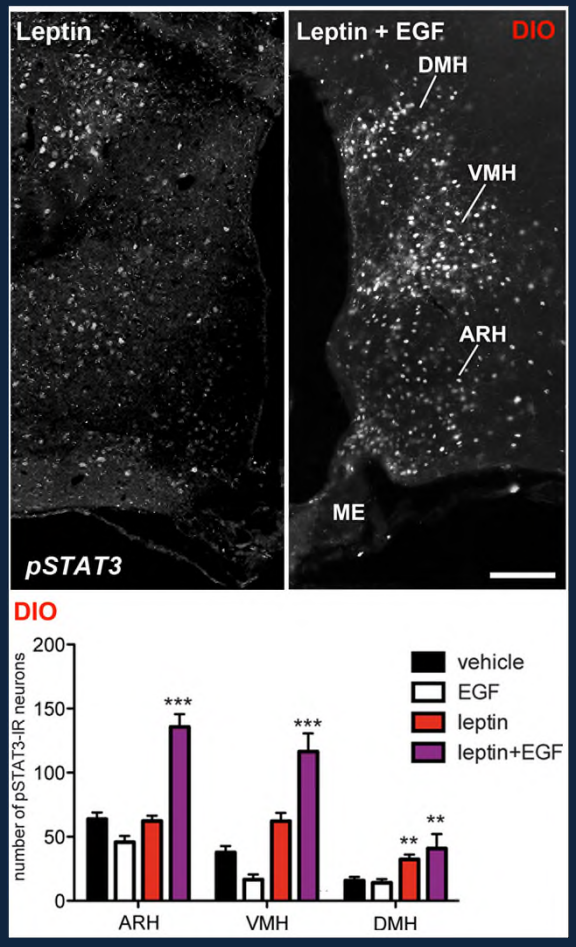
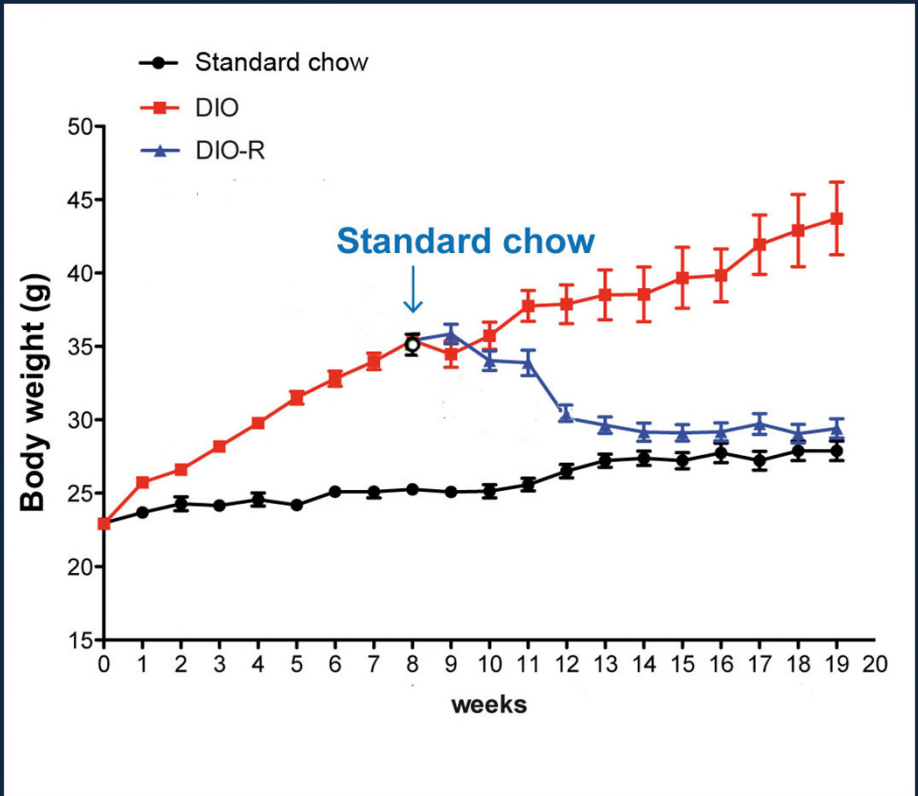




Balland et al., Cell Metab, 19, 293-301, 2014

Does EGF-mediated Activation of ERK Signalling in the Median Eminence impact weight loss in DIO ?



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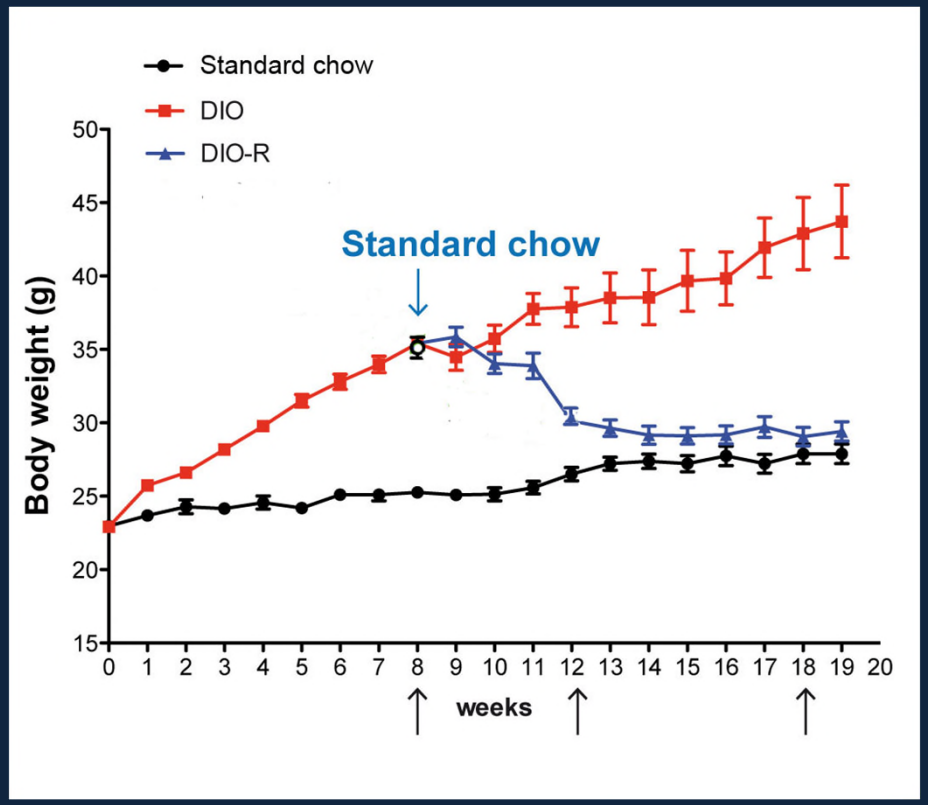

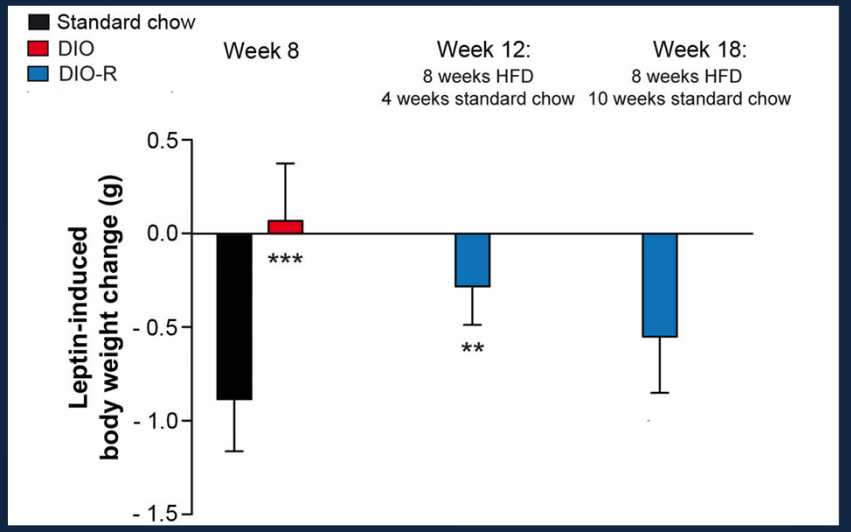

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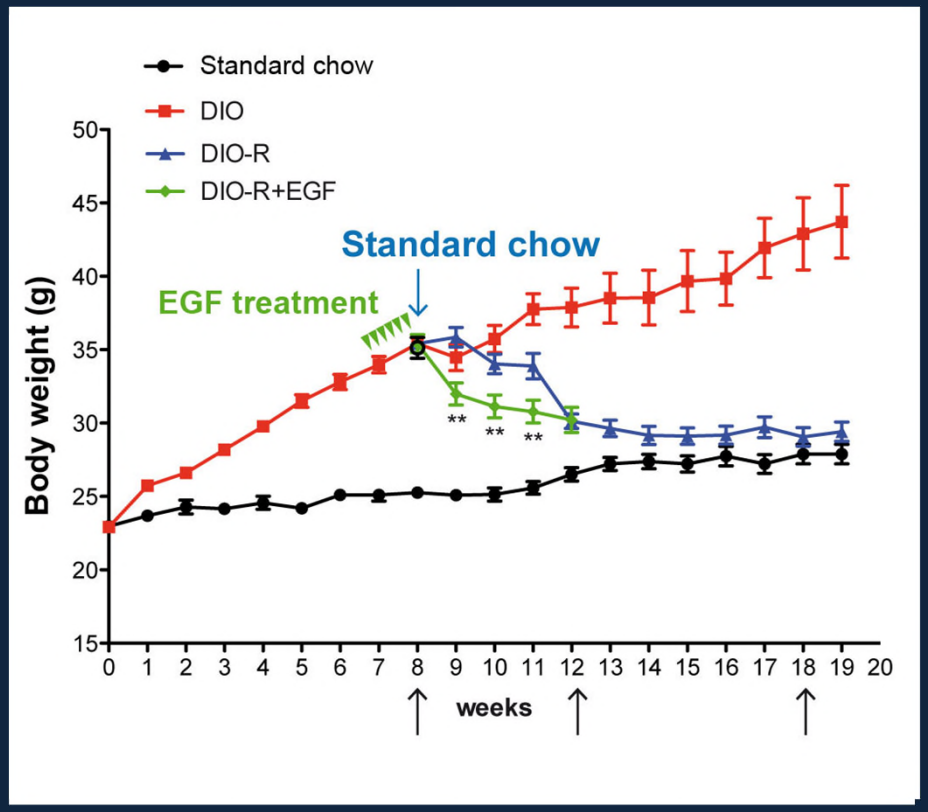
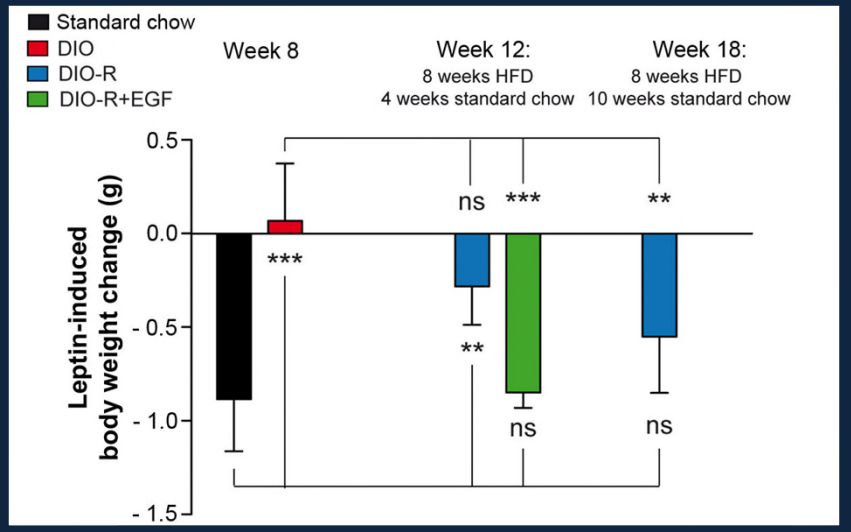
EGF-mediated Activation of ERK Signalling in the Median and Accelerates the restoration of Leptin Sensitivity in Obese Mice





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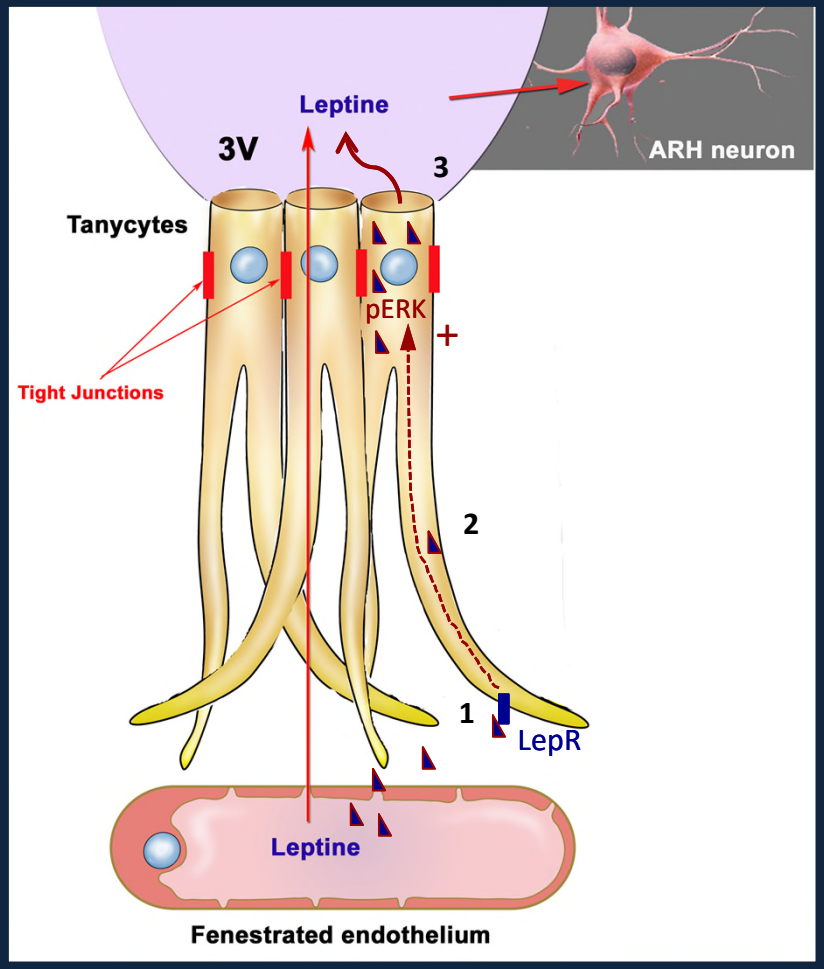
Conclusion



- The hypothalamic median eminence is a route through which leptin enters the brain
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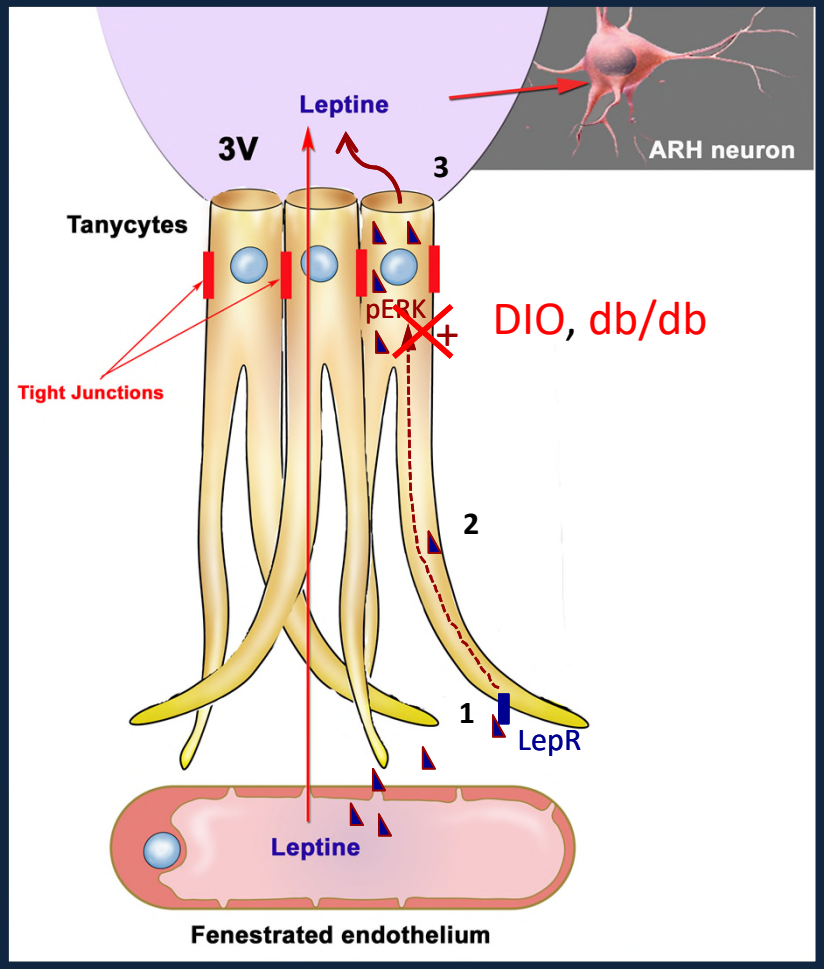
Conclusion



- The hypothalamic median eminence is a route through which leptin enters the brain
- Tanycytes act as a checkpoint along this route
- Deficient LepR-ERK signaling in tanycytes may be involved in the pathophysiology of central leptin resistance

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Acknowledgments

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