Role of Hypothalamic Tanycytes in Metabolic Homeostasis

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Conflict of interest disclosure

None
Metabolic signals and energy homeostasis

Leptin

Adipocytes

NPY/AgRP, POMC/CART

Reduce/promote food intake
Increase energy expenditure

Ghrelin

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

**Diagram:**
- Median Eminence (neuroendocrine)
- Dorsal Vagal Complex Spinal Cord (IML) (autonomic)
- Circulating metabolic signals
- Tanycytic processes
- Tight junctions
- ARH
- VMH
- DMH
- 3V
- Median Eminence
Do circulating metabolic signals have direct access to the arcuate nucleus of the hypothalamus (ARH)?

Langlet et al., Cell Metab, 17:607-617, 2013
Do circulating metabolic signals have direct access to the arcuate nucleus of the hypothalamus (ARH)?

*Langlet et al., Cell Metab, 17:607-617, 2013*
Median eminence fenestrated capillaries are permeable to circulating metabolic signals.

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

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

Mullier et al, J Comp Neurol 518:943, 2010
Do tanycytes gate the access of circulating metabolic signals into the brain?
How does Leptin Enter the Metabolic Brain?

- Median Eminence (neuroendocrine)
- Dorsal Vagal Complex Spinal Cord (IML) (autonomic)
- Leptin
- Tight junctions
- Tanycytic processes
- Fenestrated blood vessels
- Median Eminence
- 3V
- ARH
Serum and CSF leptin concentration are positively associated in lean but not obese human subjects

Serum leptin (ng/ml)

CSF leptin (ng/ml)

Linear, r=0.41, P<0.05

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
Peripherally Administered Leptin Sequentially Activates pSTAT3 in Median Eminence Followed by MBH. Tanycytes Appear to be the First Cell Type Sensing Leptin

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

**WT**

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<tr>
<th>Vehicle</th>
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- 80KDa

**pSTAT3**, **HuC/D**, **Hoescht**
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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- **pSTAT3**: - 80KDa
- **STAT3**: - 80KDa
- **Leptin**: - 16KDa

*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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- pSTAT3: ~80KDa
- STAT3: ~80KDa
- Leptin: ~16KDa

LAN: leptin with an inactivating point mutation

Balland et al., Cell Metab, 19, 293-301, 2014
The access of blood-borne leptin to the CSF is required for STAT3 activation in neurons of the mediobasal hypothalamus.
Serum and CSF leptin concentration are positively associated in lean but not obese human subjects.
Kinetics of the alteration of the transport of leptin across the blood-CSF barrier in diet-induced obesity?

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

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

$r=0.65, p<0.0001$
Plasma leptin is positively associated with body weight in minipigs fed on a high fat diet (HFD), but not CSF leptin.

**Graphs:**
- **Left graph:** Scatter plot showing the association between plasma leptin (ng/ml) and body weight (kg). The correlation coefficient is $R=0.65$, $p<0.0001$.
- **Right graph:** Scatter plot showing the association between CSF leptin (ng/ml) and plasma leptin (ng/ml). The correlation coefficient is $R=0.14$, $p=0.27$.
- Additional graph with correlation coefficient $R=0.37$, $p=0.03$.

*Chmielewski et al in preparation*
Plasma leptin is positively associated with body weight in minipigs fed on a high fat diet (HFD), but not CSF leptin.
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)

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

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**DIO** (8 weeks)

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**db/db**

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Balland et al., Cell Metab, 19, 293-301, 2014
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.
Tanyocytes 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
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
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 \textit{in vivo}?
EGF-mediated Activation of ERK Signalling in the Median Eminence

Balland et al., Cell Metab, 19, 293-301, 2014
EGF-mediated Activation of ERK Signalling in the Median Eminence restores Leptin Transport into the Hypothalamus

Balland et al., Cell Metab, 19, 293-301, 2014
EGF-mediated Activation of ERK Signalling in the Median Eminence restores Leptin Transport into the Hypothalamus

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?

[Graph showing weight gain over weeks for Standard chow, DIO, and DIO-R conditions.]

*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?

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

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[Graph showing body weight changes over weeks for different conditions, with annotations for standard chow, DIO, and DIO-R groups.]

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Balland et al., Cell Metab, 19, 293-301, 2014
EGF-mediated Activation of ERK Signalling in the Median and Accelerates the restoration of Leptin Sensitivity in Obese Mice

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

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

• Tanycytes act as a checkpoint along this route

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

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

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