Insulin action in tanycytes gates insulin uptake in the mediobasal hypothalamus and hormonal regulation of AgRP neurons

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Identification of insulin action in the central nervous system and specifically the mediobasal hypothalamus (MBH) has set the ground for the importance of proper access of peripheral insulin to the brain to regulate systemic glucose homeostasis. Furthermore, for decades classical components of blood brain barrier such as brain vascular endothelial cells have been implicated in insulin uptake in the brain. While this still may be true for brain regions relying on highly restrictive blood brain barrier, the MBH has been characterized by increased permeability for blood born molecules. Furthermore, recent studies have implicated a novel cell type, tanycytes, to be involved in regulating, fat metabolism and systemic insulin sensitivity and also to sensing peripheral hormones, glucose and nutrients. However, it remains to be investigated, which cell types are involved in insulin access to the metabolically relevant regions.

Here, mouse models with inducible insulin receptor inactivation in tanycytes and brain vascular endothelial cells (BVEC) are described. While BVEC specific IR knockout mice displayed unaltered systemic glucose metabolism, tanycyte specific IR knockout mice, however, exhibited substantial impairment in insulin sensitivity, hepatic glucose production and overall impaired response to nutrients and hormones. The blunted response to insulin in MBH of tanycyte specific IR knockout mice was comparable with diet-induced obese mice, thus, further supporting that tanycyte insulin resistance and lack of insulin uptake in the arcuate nucleus alters neurocircuits to promote obese phenotypes.

Taken together this study points towards a novel role for insulin action and resistance in tanycytes possibly contributing to multiple manifestations of obesityassociated insulin resistance.