Abstract

The blood-brain barrier (BBB) is a selective-permeable border composed of endothelial cells, mediating the communication between the periphery and the central nervous system (CNS) while preventing circulating solutes from non-selectively entering the extracellular fluid of the CNS. Acute transition to high-fat diet (HFD) feeding is accompanied by rapid changes in the molecular architecture of the BBB, BBB permeability, and brain glucose uptake. Specifically, three days of HFD feeding is sufficient to decrease glucose transporter Glut1 expression in BBB vascular endothelial cells (VECs) and reduce brain glucose uptake in mice. Nevertheless, the molecular mechanism(s) underlying these processes remain poorly defined. To identify molecular changes in the BBB associated with HFD feeding, we performed single nucleus sequencing and ribosomal profiling of the transcriptome in BBB VECs of mice after short-term HFD exposure. We found that rapid downregulation of Notch signaling following HFD feeding precedes the reduction of BBB VEC Glut1 expression. Notch activation using the Notch ligand Delta-like 4 (Dll4) restored Glut1 expression and glycolysis in cultured VECs treated with serum from HFD-fed mice. Selective, inducible expression of the Notch-IC in BBB VECs prevented the HFD-induced reduction of Glut1 expression and hypothalamic glucose uptake *in vivo*. Moreover, HFD-fed NotchIC^{BBBVEC} mice display a reduction in *Caveolin-1* expression, caveolae formation, and BBB permeability, which alters hypothalamic insulin transport, insulin action, and systemic insulin sensitivity. Collectively, this thesis highlights the critical role of Notch signaling in BBB VECs upon short-term dietary transitions and suggests that pharmacological modulation of Notch1 to reverse hypothalamic glucose uptake during HFD feeding may provide a novel strategy to counteract obesity onset.