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Thoughts on Obesity and Brain Glucose

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Homeostatic control of brain metabolism is essential for neuronal activity. Jais et al., (2016) report that reduced brain glucose uptake elicited by a high-fat diet self-corrects by the recruitment of peripheral, VEGF-producing macrophages to the blood-brain barrier. Their findings further suggest that restoring brain glucose availability might help protect from cognitive impairment in Alzheimer's disease.

With populations aging worldwide, we are witnessing an increased incidence of systemic illness linked to metabolic disease, including vascular disease and dementia (Barnes and Yaffe, 2011). Disease processes linked to metabolism may start well before old age. For example, a major risk factor for the development of Alzheimer's disease in young males is midlife obesity (40–45 years of age) (Whitmer et al., 2008). Other brain disorders including bipolar disorders and depression have been associated with metabolic dysfunction, albeit mechanistic links have remained elusive. Despite these links, the brain has long been considered a niche unto its own and underlying this is the core assumption that the blood-brain barrier acts as an almost impenetrable wall that isolates the brain from swift changes in metabolic conditions. Such thinking has confined the mechanisms responsible for age-related neurodegenerative disorders to local pathological processes and thus has delayed the awareness that systemic inflammatory processes or local immune responses in the brain may be major factors (Heneka et al., 2013). This perspective is further challenged by new findings in this issue by Jais et al. (2016), unveiling an intriguing loop between brain glucose homeostasis, systemic metabolism, and obesity that may contribute to the propensity of obese subjects to develop Alzheimer pathology.

It has long been known that insulin crosses the blood-brain barrier and that insulin receptors mediate insulin function in the brain. The identification of insulin signaling pathways and of glucose transporters regulated by insulin on brain cells has not only confirmed that metabolic control is essential for brain function but that brain function can in turn modulate systemic metabolism (Brüning et al., 2000). Moreover, there are relays (such as leptins) that convey information to the brain on the organism energy stores, which allows for neuronal control of energy balance. Leptins and other fat-tissue generated cytokines (adipokines) are elevated in obese individuals, and it is recognized that obesity itself triggers chronic inflammation, which alters innate immune system responses and eventually results in brain insulin resistance.

While these observations strongly suggest a connection between metabolic disease, inflammation, and brain diseases, a clear mechanistic understanding has remained elusive. Jens Brüning and his colleagues now unveil the processes that may explain how brain homeostatic control enslaves systemic responses involving vascular endothelial growth factor (VEGF) to restore brain glucose metabolism and prevent loss of function (Jais et al., 2016). They provide evidence that Alzheimer's pathology in obese mice can be exacerbated by deletion of VEGF in myeloid cells and propose that raising VEGF levels may be a homeostatic protective mechanism to delay or prevent cognitive impairment in obesity.

The study shows that transient feeding of mice with a high-fat diet suppresses the expression of the glucose transporter GLUT-1 at the blood-brain barrier, which results in a reduced brain glucose uptake. However, if the high-fat diet is prolonged, the defect is corrected and levels of GLUT-1 are recovered. Along with the recovery, the authors find that macrophages at the blood-brain barrier increase their expression of VEGF. Genetic reduction of GLUT-1 increases circulating levels of VEGF in lean mice, and deletion of VEGF in myeloid cells reduces levels of GLUT-1 and brain glucose uptake. Moreover memory formation is impaired in obese, but not in lean mice with myeloid VEGF deficiency. Finally, significantly faster progression of cognitive decline and neuroinflammation are seen in obese mice lacking myeloid VEGF on an Alzheimer's disease background. This supports the conclusion that reduced glucose uptake by the brain caused by a high-fat diet triggers a compensatory upregulation of VEGF production by blood-brain barrier macrophages aimed at restoring glucose uptake and preserving brain function in obese mice. Lack of VEGF in obese subjects may therefore be detrimental and favor Alzheimer's pathology (Figure 1).

The implications of these findings go well beyond a simple mechanistic link. They highlight a new systemic circuit whereby the brain recruits other organs (in this case the immune system and possibly adipose tissue) to reconstitute its glucose intake and protect its function. While the authors do not show how reduced brain glucose uptake couples with the activation of perivascular macrophages to produce VEGF, they suggest that glucose-sensing neurons via the parasympathetic system may contribute to inflammation and activation of VEGF production in macrophages.

This fascinating study raises a number of questions. Which molecule(s) are the prime effectors of high-fat diet? Hexadecanoic acid (palmitic acid) decreases

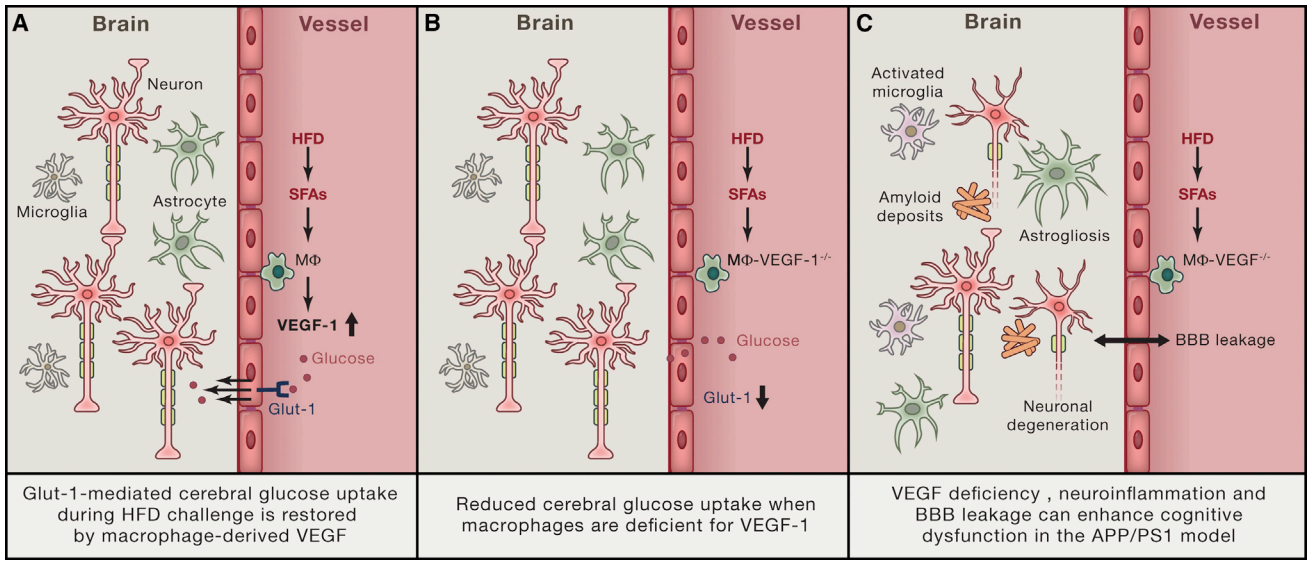

Figure 1. High-Fat Diet Stimulates a Brain-Driven Homeostatic Response

(A) VEGF restores activity of the glucose transporter Glut-1, previously downregulated by the high-fat diet (HFD) (most likely by saturated fatty acids [SFA]).
(B) The homeostatic restoration of brain glucose uptake is abolished if macrophages are VEGF deficient.
(C) VEGF deficiency exacerbates cognitive defects in mouse models of Amyloid β deposition (APP/PS1).

glucose uptake and glycolysis in brain endothelial cells, which suggests a possible role for saturated fatty acids. However, cell exposure to fatty acids may involve modification of the cell membrane in a non-selective specific manner. Experiments in vivo will be essential to clarify the possible role of saturated fatty acids as key signaling molecules that initiate the effects of the high-fat diet. Notably, under normal conditions (that is, in lean mice without a high-fat diet), myeloid-cell-derived VEGF is not required to maintain GLUT-1 expression at the blood-brain barrier, which suggests the involvement of specific factors inherent to the high-fat diet. One such factor may be a weakening of the blood-brain barrier.

It is also remarkable that restoring brain glucose uptake becomes of the utmost importance for the organism as a survival signal. Not only can recruitment of perivascular macrophages and increased VEGF concentrations restore glucose uptake in brain endothelial cells, but activation of systemic inflammation (Sabio et al., 2008) would induce a state of insulin resistance with increased blood glucose availability for the brain. The authors propose that obesity-associated inflammation would be a homeostatic mechanism to restore decreased brain glucose uptake in obese subjects.

Finally, brain glucose metabolism can be a key factor in the progression of Alzheimer's disease. The results of this study support the idea that decreased glucose uptake can exacerbate cognitive defects in APP/PS1 mice. This is in line with observations that reduction of blood-brain-barrier-GLUT1 expression leads to massive progression of Alzheimer's disease pathology in mouse models (Winkler et al., 2015). On the other hand it remains unclear whether glucose may be required for disease progression (Macauley et al., 2015). High-fat diet per se may not increase brain Aß load, but it could conceivably affect microglia function and production or assembly of oligomeric Aß. Also, the possible involvement of neuroinflammation postulated by the authors may be relevant in modifying plaque reactivity and/or oligomer production. Nevertheless, other studies (Petrov et al., 2015) have shown that high-fat diet can elicit Aß-independent effects on hippocampal learning paradigms. Thus, modulation of Aß load may be irrelevant for the high-fat-diet-induced alterations in memory function. To further substantiate this point, future studies may benefit from an assessment of plaque surface along with plaque number.

The most intriguing question in our view is whether the cognitive alterations can be reversed upon return to a normal diet. Mark Mattson and colleagues have shown that a long-term high-fat diet is able to reduce synaptic plasticity and to change the density of spines in rats (Stranahan et al., 2008), which may account for cognition defects. The hypothesis that neuroinflammation can be involved in learning defects also begs further work. In particular, given the increasing evidence for a role of the innate immune system in memory disturbances in APP/PS1 mice (Heneka et al., 2013) and the role of the innate immune system in obesity associated inflammation, it is easy to anticipate where the findings of this study may lead in the near future.

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Glia Get Neurons in Shape

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Glial cells are essential components of the nervous system. In this issue, Singhvi et al. uncover cellular and molecular mechanisms through which *C. elegans* glia shape sensory neuron terminals and thus control animal thermosensing behaviors.

Normal nervous system function requires proper assembly of numerous components, including both neurons and glia. Glia were long thought to provide passive trophic support for neurons, but in recent years their active role in regulating various aspects of neuronal function have emerged. For instance, astrocytes, the most abundant glial cell type comprising well over half of the total brain cells in mammals, can secrete a myriad of cues that regulate every stage of synapse development (Chung et al., 2015). They can also directly control the morphology of dendritic spines (Murai et al., 2003), postsynaptic structures that make up neuronal receptive endings (NREs), but how glia regulate NRE shape has remained largely unexplored. In this issue of *Cell*, Singhvi et al. uncover a mechanism by which glia actively control terminal ending shape in a subset of sensory neurons, thereby ensuring proper thermotaxic behavior in worms (Singhvi et al., 2016).

To identify glia-derived cues that regulate NREs, the authors carried out a genetic screen in *C. elegans*, which has a simplified and well-characterized nervous system with actin-enriched NREs reminiscent of vertebrate dendritic spines (Shaham, 2015). The major challenge of disentangling neuron-glia interactions is to distinguish instructive, regulatory roles from permissive, trophic support roles by glial cells. The authors elegantly addressed this issue by focusing on a specialized neuron-glia pair, AFD thermosensory neurons, and AMsh glia, in the amphid sensory organ. Like their mammalian counterparts, AMsh glia ensheathe microvilli NREs of the AFD neuron, but are dispensable for AFD survival. Through candidate and RNAi interference screens, the authors identified worms with defective AFD microvilli shapes and reduced thermosensation that harbored a mutated *kcc-3* gene, which encodes a K/Cl co-transporter (Figure 1). The authors showed that KCC-3 is expressed by and required in AMsh glia but not AFD neurons for AFD microvilli morphogenesis. Interestingly, KCC-3 proteins localize in a specialized AMsh glia microdomain that surrounds AFD NREs, but not in nearby regions where other sensory NREs are embedded, suggesting specificity in regulation. Importantly, supplying *C. elegans* culture medium with high levels of KCl restores *kcc-3* mutant phenotypes, showing that glial KCC-3 controls NRE morphology by regulating K^+ and Cl^- levels.

How does altered extracellular ion concentrations disrupt NRE microvilli morphology? One possibility is that altered ion concentration substantially changes AFD activity, which in turn reshapes microvilli morphology. Surprisingly, the authors demonstrated that neuronal activity plays little role in sculpting NRE microvilli; mutants with defective cyclic nucleotide gated channels (CNGs), which allow for cation flow across the membrane and is required for AFD activity, have largely unaffected microvilli morphology. In addition, CNG channel mutations do not rescue *kcc-3* mutant phenotypes, showing that KCC-3 must regulate NRE microvilli through a separate mechanism.

To determine the mechanism mediating neuronal response to glial KCC-3, the authors took a candidate approach and analyzed several mutants with mutations in receptor guanylyl cyclases (rGCs), a family of cell surface proteins that synthesize cGMP and are critical for *C.elegans* thermotaxic behavior. They uncovered that several rGCs are expressed by AFD sensory neurons, and that the loss-of-function of only one rGC, *gcy-8 (tm949),* rescues *kcc-3* mutant phenotypes. The authors further demonstrated that GCY-8 activity is critical for AFD NRE shape, since *gcy-8* gain-of-function mutation (*ns335*) elevates intracellular cGMP levels and causes