nature

REVIEWS

*Nature Reviews* referee guidelines

Perspective articles

*Nature Reviews* publishes timely, authoritative articles that are of broad interest and exceptional quality. Thank you for taking the time to help us to ensure that our articles meet these high standards.

Perspective articles provide a forum for viewpoints and opinionated discussions of a field or topic, describe historical foundations and influence, emerging research trends and techniques, and ethical, legal and societal issues. These articles are targeted towards readers from advanced undergraduate level and upwards and should be accessible to readers working in any discipline.

Please submit your report in narrative form and provide detailed justifications for all statements. Confidential comments to the editor are welcome, but it is helpful if the main points are stated in the comments for transmission to the authors.

Please note that all *Nature Reviews* articles will be thoroughly edited before publication and all figures will be redrawn by our in-house art editors. We therefore request that you concentrate on the scientific content of the article, rather than any minor errors in language or grammar.

Please consider and comment on the following points when reviewing this manuscript:

• Is the article timely and does it provide a useful addition to the existing literature?

• Are the scope and aims of the article clear?

• Are the ideas logically presented and discussed?

• Is the article accessible to a wide audience, including readers who are not specialists in your own field?

• Does the article clearly express an opinion, while still being fair and accurate? Although this article is an Opinion article, the authors should not ignore alternative points of view. However, please bear in mind that it may not be possible to cover all aspects of a field within such a concise article.

• Does the article provide new insight into recent advances?

• Do the figures, boxes and tables provide clear and accurate information? Are there any additional or alternative display items that you think that the authors should include?

• Are the references appropriate and up-to-date? Do they reflect the scope of the article?

• Are you aware of any undeclared conflicts of interest that might affect the balance, or perceived balance, of the article?

**The interactions between energy homeostasis and neurovascular plasticity**

**Bandy Chen1\*, Elisa de Launoit2, David Meseguer1, Cristina Garcia Caceres3,4, Anne Eichmann1,5,6, Nicolas Renier2, and Marc Schneeberger1,7\***

1 Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT, USA

2 Sorbonne Université, Institut Du Cerveau-Paris Brain Institute-ICM, Inserm U1127, CNRS UMR 7225, Paris, France

3 Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Munich & German Center for Diabetes Research (DZD), Neuherberg, Germany

4 Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians-Universität München, Munich, Germany

5 Cardiovascular Research Center, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

6 Paris Cardiovascular Research Center, Inserm U970, Université Paris, France

7 Wu Tsai Institute for Mind and Brain, Yale University, New Haven, CT, USA

**Correspondence:**

Bandy Chen, Email: [bandy.chen@yale.edu](mailto:bandy.chen@yale.edu)

Marc Schneeberger Pane, Email: [marc.schneebergerpane@yale.edu](mailto:marc.schneebergerpane@yale.edu)

**Abstract**

Food intake and energy expenditure are sensed and processed by multiple brain centers to uphold energy homeostasis. Recent evidence points to the brain vasculature as a new critical player of energy balance regulation in close association with the local neuronal networks. Nutritional imbalances alter many properties of the neurovascular system, thus suggesting the existence of a bidirectional link between our nutritional milieu and neurovascular health. The Western diet and sedentary lifestyle are responsible for the current obesity epidemic, underscoring a pressing need to create innovative and effective interventions with urgency. Emerging pharmacological interventions (e.g., GLP-1 agonism) successfully trigger weight loss. However, whether these approaches can reverse the detrimental effects of prolonged exposure to the Western diet apart from weight loss and maintain long-term weight loss in addition to possible side effects associated with chronic use need to be clarified. Lifestyle interventions do revert the nutritional trigger and positively impact our overall health, including the cardiovascular system. Hence, they emerge as powerful tools to restore brain physiology by promoting a healthy neurovascular system. In this perspective, we examine how lifestyle interventions impact the neurovascular system and neuronal networks to identify new ways to treat energy balance disorders.

**Introduction**

The dynamic interplay between the brain and body in maintaining an energy balance is a sophisticated machinery involving complex and redundant neuronal circuits, which ensure a species survival1. These circuits sense and integrate signals from the body, thereby modulating internal homeostasis and driving appropriate responses. Key to this communication are circulating factors (i.e., nutrients, hormones, and metabolites) conveyed by the bloodstream2, alongside direct neural inputs from the peripheral nervous system3. The efficacy of these signals in reaching specific brain loci hinges on their diffusion properties and the permeability of the blood-brain barrier (BBB)4.

The BBB, a critical diffusion barrier, emerges embryonically during the maturation of cerebral endothelial cells5. This maturation process selectively restricts trafficking routes through the endothelium while maintaining specific transport mechanisms. This barrier is an integral part of the neurovascular unit (NVU)6, a complex assembly of pericytes, fibroblasts, astrocytes, smooth muscle cells, and neurons in varied proportions, and which further controls and restricts the routes available to molecules from the bloodstream to the neural cells. Therefore, the NVU’s composition, which varies across brain regions and over time7, plays a pivotal role in determining how brain circuits sense circulating factors. Consequently, alterations in the molecular and cellular composition of the BBB could profoundly impact the brain’s response to feeding cues and as a result disrupt energy homeostasis.

Beyond the BBB, the cerebrovasculature possesses two additional properties that could influence how neural cells sense nutrient fluctuations. First, the local cerebral blood flow (CBF), which adapts in response to neuronal activity and metabolic demands, ensures both an adequate nutrient supply and waste removal through neurovascular coupling (NVC)8. Alterations to CBF have been often documented in pathological conditions and may affect circuit functions by compromising NVC6. Secondly, the cerebral vascular network’s structure and density vary significantly across brain regions, with brain nuclei involved in energy homeostasis often exhibiting high vascularization densities9,10. This suggests that vascular density might be fundamental to modulate the function and activity of neurons confined in brain regions responsible for nutrient sensing. This hypothesis has been largely underexplored and could establish new horizons in the modulation of energy homeostasis. The development of novel techniques to explore neurovascular plasticity has rendered this long-standing formidable task achievable (Box 1).

This perspective contrasts recent work to emphasize the need of exploiting the link between neurovascular interfaces and energy homeostasis in health and disease. We outline how these underexplored mechanisms can be harnessed for innovative therapeutic interventions, shedding light on a domain where the interplay of vascular, neuronal, and metabolic factors converges to regulate critical aspects of brain function and overall health.

**Neurovascular control of energy intake and its alterations in obesity**

Multiple studies have focused on the involvement of the vasculature, together with its associated glial cells in the control of energy homeostasis. Two major glial cell types, which lie at the interface between the blood and neurons have been identified to play a major role in modulating neurovascular plasticity to control food intake: tanycytes and astrocytes.

The arcuate nucleus of the hypothalamus (ARH) is the major hub in the central nervous system controlling energy homeostasis11. Its privileged location at the midline of the ventral hypothalamus positions it at a strategic nexus to sense circulating nutrients. Importantly, it is located between the median eminence (a circumventricular organ containing fenestrated capillaries), and the third ventricle which allows direct access to cerebrospinal fluid (CSF). There, tanycytes, a specialized population of glial cells lining the ventricle wall, form a plastic barrier ventral to the ARH that selectively exposes or shields its neurons from circulating compounds in the bloodstream and CSF12. Low glucose levels increase the permeability of this barrier via the expression of tanycytic vascular endothelial growth factor (VEGF)-A13, whereas the specific ablation of tanycytes in the region induces obesity in male mice14. Interestingly, the permeability of the fenestrated capillaries of the median eminence can also be directly modulated by distant melanin concentrating hormone neurons of the lateral hypothalamic area, capable of producing VEGF-A15. This demonstrates circular interactions between blood vessels, tanycytes, and neurons in the sensing of circulating nutrients. Investigating how the plasticity of tanycytes constitutes a bridge between neural cells and permeable blood vessels in the circumventricular organs holds considerable promise to modulate the brain control of food intake.

In the ARH and throughout the brain, astrocytes are a major component of the NVU in nutrient sensing. Astrocytes establish end-feet that are in close apposition with surrounding microvessels, generating a complete coverage of virtually all cerebral capillaries16. They respond to nutrients and hormones and regulate the accessibility of these components to couple energy availability with the activity of neurocircuits involved in metabolic control10,17. The close association of astrocytes with vascular beds in the mediobasal part of the hypothalamus renders them particularly susceptible to peripheral metabolic changes in physiological conditions, or their alterations during obesity10 (Fig.1). This influence fosters adaptations aimed at preserving energy homeostasis through their intricate interactions with the vasculature in circumventricular organs, which can alter blood vessel integrity and permeability in a dynamic way10,18.

Therefore, chronic overnutrition leading to obesity affects astrocytic functions in a multifaceted and remarkably diverse manner. Because of their importance in the makeup of the NVU, astrocytes could be one of the prime suspects linking obesity to cognitive impairments, through the disruption of vascular integrity and permeability. For instance, in diet-induced obesity, elevated leptin levels in the circulation have been shown to trigger the release of soluble factors such as astrocytic-derived VEGF, leading to alterations in the integrity and permeability of vascular beds and angiogenesis at the level of the microvasculature in both obese mice and humans10,18. This increases the leakiness of the parenchymal barrier to both the humoral and CSF circulation. Moreover, the loss of insulin receptors in astrocytes leads to reduced expression of glucose transporter 1 (GLUT1), resulting in restricted delivery of glucose into the brain19,20. Similarly, a hypercaloric diet induces transient alterations in brain glucose uptake by modulating GLUT1 expression on vascular endothelial cells21. These studies propose that the impact of glial cell-derived VEGF is crucial for sustaining brain glucose uptake. Improving its uptake by favoring high VEGF expression can alleviate cognitive impairments associated with obesity21.

Another important way neural cells can control nutrient sensing from the bloodstream is by modulating the CBF via NVC. When neural activity locally increases in response to nutrient sensing or humoral fluctuations, CBF in the active regions is enhanced22. It is generally thought that an increased blood flow is necessary to deliver the oxygen required to sustain brain functions during periods of elevated activity. However, changes in nutritional patterns could also underlie a supraphysiological support of key feeding neurons, ultimately sustaining their activity and reinforcing an increase in feeding. By understanding how NVC responds to nutrient sensing and other cues related to energy intake, we may uncover alternative mechanisms participating in appetite regulation.

Obesity-induced changes in CBF can partly explain how chronic overnutrition interferes with nutrient sensing in the brain, which persists even after weight loss23. Indeed, in middle-aged and older adults, a higher BMI is associated with lower hippocampal CBF and cerebrovascular reactivity (CVR), the capacity of the brain’s vasculature to alter CBF in response to a stimulus24,25. The impact of obesity on CBF is more potent than aging, with an increase in waist circumference of 1.3 cm linked to the same reduction in CBF as 1 year of advanced aging26.

Plastic changes to NVC during nutrient shifts have been extensively studied in preclinical models. High glucose levels have been found to affect both NVC and cerebrovascular patterning, due to alterations in BBB integrity27. Hyperglycemia-induced neuronal activity leads to an elevated CBF as a compensatory mechanism. However, this prolonged effect may trigger a negative feedback mechanism, impairing nutrient sensing, neuronal activity, and NVC28. Exposure for 8 weeks to high fat diet (HFD) reduces the functional hyperemia that follows whiskers stimulation in the mouse, suggesting a reduction in the strength of cortical NVC early after a dietary shift29. These findings suggests that metabolic abnormalities occur earlier in the brain compared to the periphery. In rats, a short-term cafeteria diet, consisting of grocery store-purchased highly-processed food items, for 12-16 weeks increases resting CBF in the hippocampus and reduces CVR. This happens without impacting learning and memory30,31. Memory deficits are however seen after a long-term cafeteria diet (30 weeks)30,31. These variations can be attributed to the duration of the cafeteria diet, leading to different levels of metabolic dysfunction. Both conditions do not induce changes in the density of CA1 neurons, structural vascular alterations, nor alter cerebrovascular integrity, suggesting that changes in CBF and volume are more functional than structural. It would be important to determine in such models whether changes to the CBF are solely linked to a shift in the plasma concentration of nutrients or signaling factors, or if chronic changes to neural activity levels in specific regions also plays a direct role.

Investigating the onset and duration of obesity in relation to NVC and cerebrovascular rewiring will provide a timeline to understand the brain’s adaptation to overnutrition. Moreover, the impact of obesity on CBF goes beyond nutrient sensing, as metabolic abnormalities contribute to a heightened risk of ischemic stroke32 or silent brain infarcts33. Higher adiposity in midlife is also associated with small vessel disease, leading to changes in white matter, impacting both subcortical and cortical regions, resulting in cognitive deficits34. In summary, obesity significantly impacts the brain’s vascular system, disrupting the exchange of metabolic signals between the periphery and the brain, therefore compromising both the ability of the brain to regulate energy homeostasis and overall brain health35.

**Sexual dimorphism in the neurovascular landscape**

Sex differences exert significant influence on the development and progression of the neurovascular landscape36. In cortical regions, young women demonstrate higher CBF than young men in the frontal and parietal lobes, with differences shrinking after age 65 indicating a greater decline in CBF for women37,38. On the other hand, age-related decline in BBB function of cortical regions is found to be more significant in men39. From epidemiological studies, sexual dysmorphisms are seen in the prevalence of metabolic and neurological disorders40. Men are at a greater risk for vascular complications associated with cognitive impairment and dementia41. The discrepancies in the neurovascular landscape and susceptibility to neurological disorders can be explained by the difference in hormonal and metabolic profiles. Both estrogen and androgens promote angiogenesis and cerebrovascular remodeling42. Estrogen decreases cerebral vascular tone and increases CBF, while androgens increase cerebral vascular tone and decrease CBF. The difference in body composition and hormonal profile between sexes contribute to a different metabolic profile, resulting in divergent downstream effects on the neurovascular landscape (Table 1). Understanding the role of hormones, metabolites, and nutrients on the rewiring of the neurovascular landscape will enhance our grasp on the impact of sex differences and pathological states (states of varied metabolic profile) on the neurovascular landscape.

**The impact of lifestyle interventions on neurovascular health**

With the surging occurrence of neurometabolic disorders, lifestyle interventions have advanced toward clinical implementation through dietary adjustments. Lifestyle intervention encompasses a range of activities aimed at enhancing the overall quality of life and reducing the risk of various chronic diseases43. The most effective interventions for managing metabolic and neurological risk factors involve intermittent fasting (IF), caloric restriction (CR), and physical activity (PA)44. The beneficial impact of IF, CR and PA on peripheral and central metabolism responsible for energy homeostasis has been profoundly reviewed45,46. Here, instead, we will focus on the mechanisms through which these interventions enact their benefits on neurovascular health (Fig.2).

Intermittent fasting

Fasting triggers a transition from a sated state to a hunger state. This transition has a deep impact on neuronal activity and vasomotricity, which is visible at the level of whole-brain functional connectivity and regional CBF47. High-field functional MRI studies reveal specific patterns of functional connectivity during fasting, particularly in the hippocampus-cortex pathway, that may reinforce our urge for food47. IF has gained attention in recent years for its potential in weight management and addressing metabolic disorders. Periodic metabolic switching from glucose to ketones provide evolutionarily conserved responses that enhance metabolism and reduce inflammation48. While its effects on metabolic and cognitive functions in healthy, lean individuals are relatively modest49, the benefits of IF in aging and pathological states are significant48. For instance, a shortened eating window in middle-aged adults has shown promise in reducing the risk of cognitive impairment50. Furthermore, early time-restricted feeding in prediabetic individuals significantly improves various metabolic parameters including insulin levels and sensitivity, blood pressure, and oxidative stress51. Among older adults with mild cognitive impairment (MCI), IF over 36 months notably enhances cognitive performance52. In sum, the neuroprotective role of IF in humans is evident.

In young mice, 3 months of IF yields remarkable effects on hippocampal neurogenesis and long-term potentiation of hippocampal synapses53. In aged mice, alternate day IF for 6 weeks reverses in dissociated neurons age-related synaptic changes in Ca2+ buffering and inhibitory transmission, albeit without mitigating cognitive impairments *in vivo*54. Beyond these limited neurophysiological observations, several pieces of evidence point to a positive impact of IF on neurovascular functions. For instance, preconditioning with IF over 16 hours of fasting for 4 months results in a substantial reduction in chronic cerebral hypoperfusion-induced neurovascular pathologies55. This reduction is achieved by attenuating microvascular leakage, enhancing BBB integrity, preventing tight junction breakdown, reducing white matter injury, and minimizing neuronal loss55. Additionally, in a rat model featuring middle cerebral artery occlusion (MCAO), 3 months of preconditioning with IF ameliorates neurological severity score and adhesive removal test and increases microvessel density56. Moreover, in mice that suffer from subcortical vascular dementia, postconditioning with IF for a month significantly attenuates cognitive impairments and neuronal loss without impacting the cerebrovasculature and white matter57.

These findings suggest that further investigations into the impact of IF on NVC in brain regions controlling energy homeostasis may yield interesting insights into its mechanisms of action, which are yet to be elucidated. Preclinical models should be used to elucidate the cellular and molecular impact of IF on the NVU, and whether this translates into a positive feedback loop on neurometabolic functions. To fully harness the potential of IF as an interventional tool, it is imperative to explore its effects in a variety of settings, using different models of pre- and postconditioning across various age groups. This comprehensive approach is essential to uncover the full spectrum of benefits and limitations associated with IF and neurological health.

Caloric restriction

The mechanistic link between food intake and neurovascular functions is better understood in models of CR. In rodents, most CR models range from 10 to 50% of CR from baseline, while in humans, most interventions aim for 10-25% CR per day46. CR leads to reductions in neuroinflammation and oxidative stress58. In healthy non-obese adults, a two-year regimen of CR leads to significant improvements in working memory59,60. Notably, the benefits of CR extend beyond these healthy populations to individuals with various medical conditions. For patients with multiple sclerosis, a 12-week CR plan results in improved brain health61, associated with elevated regional CBF in the bilateral inferior temporal gyri and bilateral fusiform gyri61. The underlying mechanisms still necessitate further clarification.

Preclinical studies suggest that the neuroprotective effects of CR involve NVC. In young mice, CR enhances CBF and improves BBB function by inhibiting mTOR expression and enhancing eNOS signaling62. These effects are also observed in aged mice, where CR helps maintain CBF in the hippocampus and frontal cortex, thereby preserving learning and long-term memory, and reducing anxiety62. In aged rats, 6 months of CR enhances vascular tone in cerebral and mesenteric arteries, with minor effects on vascular remodeling63. Moreover, in diet-induced overweight rats, 12 weeks of CR improves BBB leakage and glial activation by reducing neurogranin-associated calcium signaling64. When CR is prolonged in an aged and obese rat model, it improves oxidative stress and inflammation and increases plasma adiponectin levels65. As an insulin sensitizer, adiponectin plays a fundamental role in vascular physiology by regulating glucose uptake66. Disrupted adiponectin signaling is reported in various neurovascular diseases, therefore the capability of CR to ameliorate plasma adiponectin levels points to a possible mechanism through which CR enacts its neuroprotective effects66.

Studies that investigate the potential of CR in neuroprotection encompass a range of neurological diseases. Even in mice at a very early age (postnatal day 7), moderate CR offers protection against hypoxic ischemia, with benefits attributed to the suppression of p53 expression in the NVU67. This suppression leads to reduction in neurovascular damage and a decrease in microglia activation67. A preconditioning approach with 4 weeks of CR protects against transient focal ischemia-induced infarct by enhancing glucose metabolism and promoting adiponectin secretion68. In aged rats, an 8-week program of CR preceding experimental infarction prevents stroke-induced weight loss and enhances overall behavioral and metabolic recovery69. This protective effect is suggested to be partly mediated through gut microbiota70. In a mouse model of transient MCAO, postconditioning with 3 days of CR reduces infarct volume, while postconditioning with 56 days of CR promotes recovery in post-ischemia motor coordination71. This approach increases long-term neuronal survival, brain capillary density and reduces brain atrophy in the peri-infarct striatum71. Unraveling the mechanisms underlying CR-induced neuroplasticity necessitate further examination to understand the intricate interplay between circulating metabolites and modifications to the NVU structure.

The impact of both IF and CR on obesity depends on the reversibility of obesity-induced neurovascular decoupling, cerebrovascular rewiring, and cognitive decline. This likely hinges on the severity of obesity. However, studying how the neurovascular system reacts to these interventions in the context of obesity may help to reverse its long-term alterations. Practicing IF and CR in overweight and obese adults enhances cognitive performances in tasks thought to involve hippocampal functions, albeit no differences are seen between the CR and IF regimen72,73. Among obese patients with MCI, a 12-month CR regimen leads to improvements in memory, executive function, global cognition, and language74. This improvement was more pronounced in younger seniors and carriers of the APOE4 allele, a variant of the APOE gene causing vascular defects associated with Alzheimer’s Disease74. In midlife adults with overweight and obesity, a 12-month intervention involving diet and exercise leads to a 10% weight loss and increased CBF in frontal, parietal, and subcortical regions75. Intriguingly, the combination of diet and exercise appears to modulate the CBF in a region-specific manner75.

Physical activity

Energy homeostasis is achieved through an intricate balance between energy intake and energy expenditure. Akin to energy intake, energy expenditure takes various forms including basal metabolic rate, thermogenesis, and PA76,77. While basal metabolic rate and thermogenesis are vital components of energy expenditure, in the context of NVC, most evidence highlights the significance of PA78. Moreover, PA is tunable in a voluntary manner. PA has emerged as a key lifestyle intervention in promoting cardiovascular health, reducing the risk of metabolic diseases, and extending lifespan. Beyond its physical benefits, regular exercise improves mental well-being, alleviates stress, and mitigates the risks of conditions such as dementia and depression. The recent surge in sedentary lifestyle in Western societies increases all-cause mortality and the risks for metabolic and neurological diseases79. Several PA interventions have been proposed to reduce disabilities and lengthen healthspan80. While the metabolic benefits of PA (e.g., improving blood lipid profiles) and its impact on neurological health (e.g., migraine prevention) have been thoroughly investigated81,82, the molecular mechanisms underlying the benefits of PA on the cerebral vascular system need to be deciphered.

Chronic aerobic exercise is linked to improved cognition, a reduction in depression and anxiety83,84, white matter plasticity and episodic memory performance85. PA is a widely adopted intervention to supplement pharmacology in the treatment of neurodegenerative diseases86-89. The link between PA and neuroplasticity could in part involve the upregulation of an array of neurotrophic factors, including brain derived neurotrophic factor90,91. PA for 8 weeks reinstates brain insulin sensitivity in sedentary overweight and obese adults92. CBF responses to intranasal insulin differs for overweight and obese adults, with increased CBF in the middle frontal gyrus but decreased CBF in cortico-limbic regions93. The potential of lifestyle interventions to mitigate obesity-induced neuroinflammation and insulin resistance as well as restoring various signaling pathways requires further investigation into how nutrient shifts affect NVC. The consensus in all the outlined studies is that PA in patients alters NVC and CBF, with deeper structural changes in the cerebrovasculature potentially occurring in chronic interventions.

Supporting this notion, several preclinical studies have shown that neurovascular properties are affected upon exercise. Studies in the rat motor cortex have unveiled the induction of angiogenesis, an increase in cerebral blood volume, and heightened metabolism upon exercise94. In mice, PA can prevent cerebrovascular damage and white matter loss caused by 10 months of HFD feeding95. Although PA led to weight loss, the active HFD mice remains significantly heavier than sedentary control mice95. This suggests that the benefits of PA on brain health is partly independent of weight loss. PA reduces the interaction between MBP and IBA1, limits the number of CD68+ cells, and mitigates the reduction in endothelial cells and pericytes in the frontal partial cortex and corpus callosum without significantly preventing myelin loss95. The mechanisms involved in obesity-induced neurovascular decoupling and cerebrovascular rewiring, and whether these cerebral shifts are reversible in response to lifestyle interventions require further investigation.

Still, these findings underscore a direct link between exercise and an enhanced NVC. The connection between exercise and neuroprotection is partly explained by an enhancement of the cerebral blood vessel plasticity. In a 6-month aerobic exercise intervention for middle-aged and older adults, improvements in cognitive function and cerebrovascular regulation are associated with augmentation of the vasodilatory effect mediated by CO283. Compared to sedentary individuals, active individuals have higher resting intracranial blood velocity and lower CVR in the middle and posterior cerebral arteries96,97. Both CBF and CVR decrease with age, but PA assists in preserving or enhancing these factors in healthy individuals98. A possible explanation for reduced CVR in active individuals is that chronic exposure to elevated CO2 concentration due to constant exercise results in the desensitization of the cerebrovasculature to CO2, thereby leading to a lack of vasodilation.

Together, lifestyle interventions are effective interventions to extend lifespan and healthspan, and prevention and treatment of metabolic and neurological diseases99. By alternating whole-body metabolic profile, these interventions are likely impacting the cerebral landscape through direct and indirect mechanisms. While their impact on cerebrovascular health largely overlaps, there are distinct nuances between the effects of IF, CR and PA (Table 2). Therefore, further research is required to distinguish the physiological and molecular differences with a temporal component on the onset, duration, and type of intervention. How such interventions affect cerebrovascular health from a mechanistic standpoint remains understudied. An urgent need exists to delineate the efficacy and safety of these inventions as an alternative to pharmacological treatments of the ever-increasing metabolic and neurological diseases associated with overnutrition and a sedentary lifestyle. Though pharmacological interventions lead to a greater weight loss compared to lifestyle modifications, weight regain often occurs after termination of these interventions. The addition of lifestyle modifications to complement pharmaceutical treatments will provide the opportunity to transition out of chronic usage and minimize weight rebound44.

**Conclusions**

NVC plays a fundamental role in energy balance regulation, serving as an intermediary that facilitates the communication between central and peripheral systems. Lifestyle interventions are steadily growing in popularity. Understanding their impact on cerebrovascular health strengthens their effectiveness in complementing pharmacological interventions. The uncoupling of the neurovascular network observed in obesity establishes a connection between overnutrition and cognitive decline as well as neurological diseases. Establishing stronger mechanistic links between the alterations of the neurovascular system in key brain regions and metabolic disorders, inspired by the positive effects of lifestyle interventions remains a promising avenue to complement the current available pharmacological treatments of obesity. Whether the benefits of lifestyle interventions on the neurovascular landscape are through a direct mechanism or indirectly by affecting overall weight loss remains to be elucidated. Nonetheless, it is evident that these interventions demonstrate beneficial effects on the neurovascular landscape and can be utilize as tools to combat the pathological rewiring of the neuro-glial-vascular unit and cerebrovasculature. Highlighting the importance of lifestyle modifications offer the utmost chance to prevent the development of obesity and its comorbidities.

**Acknowledgements**

M.S. acknowledges support from the McCluskey family, E. Matilda Ziegler Foundation and Interstellar Initiative (NYAS/AMED). This work was supported by the National Institute of Diabetes, Digestive and Kidney Diseases 4R00DK1208689.

**Box**

**Box 1. Advancements in the study of neurovascular plasticity**

The brain's vasculature presents a complex network of arteries, capillaries, and veins spanning various scales, from millimeter-sized to micron-sized vessels. This complexity has historically posed challenges in quantifying structural changes in cerebrovascular topology across the brain. However, recent breakthroughs in technology have revolutionized our ability to visualize and quantify vascular plasticity at molecular, anatomical, and functional levels, offering unprecedented insights into neurovascular dynamics. Volumetric and intravital imaging together with spatial transcriptomics have emerged as complementary tools to identify the spatio-temporal dynamics of the cerebral landscape.

Immunolabeling-based tissue clearing, such as iDISCO+, combined with 3D light-sheet microscopy, enables the generation of high-resolution maps detailing vessel tortuosity, length, and interruptions9. By referencing the Allen Brain Atlas, researchers can precisely identify regions of interest exhibiting hypervascularization or hypovascularization events.

Intravital imaging techniques, including functional ultrasound (fUS), have transformed our ability to capture dynamic microvasculature changes in response to brain activation with high spatio-temporal resolution100. Unlike traditional functional magnetic resonance imaging (fMRI), fUS provides superior spatio-temporal resolution, crucial for localizing vessel remodeling events.

Another advancement lies in studying the molecular significance of neurovascular topologic events within the neurovascular unit, where neuronal, vascular, and immune structures converge. Single-cell RNA sequencing (scRNA-seq) offers insights into the molecular identities of different neural cell types. However, to understand how specific configurations of cell types contribute to functional changes in remodeled brain regions require a spatial component. Spatial transcriptomics, such as visium, reveals the spatial organization of cell types and their molecular connectivity within the brain101.

Together, these advancements offer a comprehensive approach to study neurovascular plasticity, integrating structure, function, and molecular dynamics. By leveraging these cutting-edge technologies, modern neuroscience is poised to unravel the intricate adaptations of the cerebrovasculature in health and disease.

**Figure legend**

**Figure 1. Pathological rewiring of the neurovascular landscape.** Chronic overnutrition leads to excessive neuroinflammation to compensate for the continuous metabolic turnover. Pathological levels of glial activity increase BBB permeability and infiltration of peripheral immune cells, resulting in a vicious cycle of neurovascular uncoupling. Tanycytes lining up the ventricle become leaky and there is an altered inflow of CSF to the parenchyma. As a result, the impaired communication between the neuro-glial-vascular unit leads to an imbalance between afferent and efferent signals and overall energy dyshomeostasis.

**Figure 2. Lifestyle interventions on neurovascular health.** A sedentary lifestyle paired with an obesogenic milieu leads to neurovascular decoupling and microvascular dysfunction, resulting in neuroinflammation, cognitive decline, and a higher risk of neurodegeneration. This leads to a feedback loop that perpetuates excessive food intake and physical inactivity. Implementing lifestyle interventions enhances neurovascular coupling and cerebrovascular health, leading to improved cognitive function and a reduced risk of neurodegeneration.

**Table**

**Table 1.**

|  |  |  |
| --- | --- | --- |
| **Name** | **Main sources** | **Major effect on NVU** |
| **Leptin** | Adipose tissue | * Promotes angiogenesis and vascular remodelling in a region specific manner10 * Regulates astrocytic release of soluble factors, such as VEGF, to modulate BBB function and properties10 * Promotes neurogenesis and angiogenesis after stroke102, and angiogenesis via pericyte STAT3 pathway upon Intracerebral Hemorrhage103 |
| **Insulin** | Pancreas | * Modulates angiogenesis in the cortex via astrocytes in young but not in aged mice104 * Regulates neurovascular coupling: glucose uptake handling couples with blood flow via astrocytes20,104 * Both insulin and IGF-1 signaling in endothelium play a role in proliferation of retinal endothelial cells through the expression of vascular mediators105 * Pericyte insulin receptors modulate retinal vascular remodeling (vascular sprouting) and endothelial angiopoietin signaling to promote venous plexus development106 |
| **Cytokines**  (IL-1β, IL6, TNFα) | Immune cells Macrophages  Glial cells | * Regulates integrity and permeability of the BBB107 * Vascular remodelling * Enhances glia reactivity and local immune cell recruitment * Elevated levels 🡪 promotes inflammation 🡪 BBB dysruption108 |
| **Adiponectin** | Adipose tissue | * Not cross the BBB * Adiponectin receptors on brain endothelial cells 🡪 modulate cytokine secretion109 * Potential cerebroprotective action against CNS pathologies like stroke via receptor-mediated mechanisms110 |
| **Ketone bodies**  (beta-hydroxybutyrate: BHB) | Liver | * *i.v.* infusion of BHB: regulates glucose transport across the BBB 🡪 decreases in cerebral glucose consumption and increases blood flow in humans111,112 * Ketogenic diet enhances neurovascular functions: elevates cerebral blood flow, particularly in the ventromedial hypothalamus113 |
| **Lactate** | Muscle cells  Red blood cells  Glial cells | * Exercises increases lactate delivery into the brain and cerebral blood flow in humans114 * *i.v.* lactate infusion decreases brain glucose uptake and enhances oxygen consumption in humans114,115 * Lactate protects cerebral function during hypoglycemia: elevating lactate (within a normal range) significantly reduces symptomatic responses to hypoglycaemia116 |
| **Saturated fatty acids** (SFAs) | Adipose tissue | * Ingestion of SFA-enriched diets are associated with increased risk of BBB dysfunction and neurovascular inflammation117 * Natural SFAs, like lauric acid, preserve brain microvascular functions, reducing infarct volumes and brain edema during ischemic insults, even with acute hyperglycemia118 * Intra-arterially infused SFA emulsions open the BBB through tight junctions and promote drug delivery into the brain119 * *i.c.v.* SFA infusion enhances NF-κB-mediated inflammation at the BBB via TLR4 receptor120 |

**Table 2.**

|  |  |
| --- | --- |
| **Intervention** | **Major effect on NVU** |
| **Intermittent fasting** | * Attenuates microvascular leakage and tight junction breakdown, and enhances BBB integrity after cerebral hypoperfusion61 * Increases microvessel density and ameliorates cognitive function after middle cerebral artery occulsion62 * Attenuates neuronal loss after subcortical vascular dementia63 |
| **Caloric restriction** | * Enhances regional CBF and BBB function68,69 * Regulates vascular tone in cerebral and mesenteric arteries70 * Mitigates obesity-induced BBB leakage and glial activation71 * Reduces neurovascular damage and neuroinflammation after hypoxic ischemia74 |
| **Physical activity** | * Enhances regional CBF in the middle frontal gyrus and attenuates CBF in cortico-limbic regions100 * Induces angiogenesis and increases cerebral blood volume101 * Mitigates loss of endothelial cells and pericytes by reducing neuroinflammation102 * Elevates resting intracranial blood velocity and reduces cerebrovascular reactivity103,104 |

**References**

1 Myers, M. G., Jr., Affinati, A. H., Richardson, N. & Schwartz, M. W. Central nervous system regulation of organismal energy and glucose homeostasis. *Nat Metab* **3**, 737-750, doi:10.1038/s42255-021-00408-5 (2021).

2 Banks, W. A. The blood-brain barrier as an endocrine tissue. *Nat Rev Endocrinol* **15**, 444-455, doi:10.1038/s41574-019-0213-7 (2019).

3 Kim, K. S., Seeley, R. J. & Sandoval, D. A. Signalling from the periphery to the brain that regulates energy homeostasis. *Nat Rev Neurosci* **19**, 185-196, doi:10.1038/nrn.2018.8 (2018).

4 Ayloo, S. & Gu, C. Transcytosis at the blood-brain barrier. *Curr Opin Neurobiol* **57**, 32-38, doi:10.1016/j.conb.2018.12.014 (2019).

5 Langen, U. H., Ayloo, S. & Gu, C. Development and Cell Biology of the Blood-Brain Barrier. *Annu Rev Cell Dev Biol* **35**, 591-613, doi:10.1146/annurev-cellbio-100617-062608 (2019).

6 Iadecola, C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron* **96**, 17-42, doi:10.1016/j.neuron.2017.07.030 (2017).

7 Vanlandewijck, M. *et al.* A molecular atlas of cell types and zonation in the brain vasculature. *Nature* **554**, 475-480, doi:10.1038/nature25739 (2018).

8 Hillman, E. M. Coupling mechanism and significance of the BOLD signal: a status report. *Annu Rev Neurosci* **37**, 161-181, doi:10.1146/annurev-neuro-071013-014111 (2014).

9 Kirst, C. *et al.* Mapping the Fine-Scale Organization and Plasticity of the Brain Vasculature. *Cell* **180**, 780-795 e725, doi:10.1016/j.cell.2020.01.028 (2020).

10 Gruber, T. *et al.* Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab* **33**, 1155-1170 e1110, doi:10.1016/j.cmet.2021.04.007 (2021).

11 Jais, A. & Bruning, J. C. Arcuate Nucleus-Dependent Regulation of Metabolism-Pathways to Obesity and Diabetes Mellitus. *Endocr Rev* **43**, 314-328, doi:10.1210/endrev/bnab025 (2022).

12 Prevot, V. *et al.* The Versatile Tanycyte: A Hypothalamic Integrator of Reproduction and Energy Metabolism. *Endocr Rev* **39**, 333-368, doi:10.1210/er.2017-00235 (2018).

13 Langlet, F. *et al.* Tanycytic VEGF-A boosts blood-hypothalamus barrier plasticity and access of metabolic signals to the arcuate nucleus in response to fasting. *Cell Metab* **17**, 607-617, doi:10.1016/j.cmet.2013.03.004 (2013).

14 Yoo, S. *et al.* Tanycyte ablation in the arcuate nucleus and median eminence increases obesity susceptibility by increasing body fat content in male mice. *Glia* **68**, 1987-2000, doi:10.1002/glia.23817 (2020).

15 Jiang, H. *et al.* MCH Neurons Regulate Permeability of the Median Eminence Barrier. *Neuron* **107**, 306-319 e309, doi:10.1016/j.neuron.2020.04.020 (2020).

16 Hosli, L. *et al.* Direct vascular contact is a hallmark of cerebral astrocytes. *Cell Rep* **39**, 110599, doi:10.1016/j.celrep.2022.110599 (2022).

17 Marina, N. *et al.* Brain metabolic sensing and metabolic signaling at the level of an astrocyte. *Glia* **66**, 1185-1199, doi:10.1002/glia.23283 (2018).

18 Yi, C. X. *et al.* High calorie diet triggers hypothalamic angiopathy. *Mol Metab* **1**, 95-100, doi:10.1016/j.molmet.2012.08.004 (2012).

19 Hernandez-Garzon, E. *et al.* The insulin-like growth factor I receptor regulates glucose transport by astrocytes. *Glia* **64**, 1962-1971, doi:10.1002/glia.23035 (2016).

20 Garcia-Caceres, C. *et al.* Astrocytic Insulin Signaling Couples Brain Glucose Uptake with Nutrient Availability. *Cell* **166**, 867-880, doi:10.1016/j.cell.2016.07.028 (2016).

21 Jais, A. *et al.* Myeloid-Cell-Derived VEGF Maintains Brain Glucose Uptake and Limits Cognitive Impairment in Obesity. *Cell* **165**, 882-895, doi:10.1016/j.cell.2016.03.033 (2016).

22 McManus, R. *et al.* Dynamic response of cerebral blood flow to insulin-induced hypoglycemia. *Sci Rep* **10**, 21300, doi:10.1038/s41598-020-77626-6 (2020).

23 van Galen, K. A. *et al.* Brain responses to nutrients are severely impaired and not reversed by weight loss in humans with obesity: a randomized crossover study. *Nat Metab* **5**, 1059-1072, doi:10.1038/s42255-023-00816-9 (2023).

24 Amen, D. G., Wu, J., George, N. & Newberg, A. Patterns of Regional Cerebral Blood Flow as a Function of Obesity in Adults. *J Alzheimers Dis* **77**, 1331-1337, doi:10.3233/JAD-200655 (2020).

25 Glodzik, L. *et al.* Higher body mass index is associated with worse hippocampal vasoreactivity to carbon dioxide. *Front Aging Neurosci* **14**, 948470, doi:10.3389/fnagi.2022.948470 (2022).

26 Knight, S. P. *et al.* Obesity is associated with reduced cerebral blood flow - modified by physical activity. *Neurobiol Aging* **105**, 35-47, doi:10.1016/j.neurobiolaging.2021.04.008 (2021).

27 Chhabria, K. *et al.* The effect of hyperglycemia on neurovascular coupling and cerebrovascular patterning in zebrafish. *J Cereb Blood Flow Metab* **40**, 298-313, doi:10.1177/0271678X18810615 (2020).

28 Liu, J. *et al.* Cerebral Blood Flow Alterations in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Arterial Spin Labeling Studies. *Front Aging Neurosci* **14**, 847218, doi:10.3389/fnagi.2022.847218 (2022).

29 Li, W. *et al.* Early effects of high-fat diet on neurovascular function and focal ischemic brain injury. *Am J Physiol Regul Integr Comp Physiol* **304**, R1001-1008, doi:10.1152/ajpregu.00523.2012 (2013).

30 Gomez-Smith, M. *et al.* Reduced Cerebrovascular Reactivity and Increased Resting Cerebral Perfusion in Rats Exposed to a Cafeteria Diet. *Neuroscience* **371**, 166-177, doi:10.1016/j.neuroscience.2017.11.054 (2018).

31 Livingston, J. M. *et al.* Influence of metabolic syndrome on cerebral perfusion and cognition. *Neurobiol Dis* **137**, 104756, doi:10.1016/j.nbd.2020.104756 (2020).

32 Koh, I. S., Minn, Y. K. & Suk, S. H. Body Fat Mass and Risk of Cerebrovascular Lesions: The PRESENT (Prevention of Stroke and Dementia) Project. *Int J Environ Res Public Health* **16**, doi:10.3390/ijerph16162840 (2019).

33 Nam, K. W. *et al.* Obesity without metabolic disorder and silent brain infarcts in aneurologically healthy population. *Int J Obes (Lond)* **44**, 362-367, doi:10.1038/s41366-019-0372-6 (2020).

34 Morys, F., Dadar, M. & Dagher, A. Association Between Midlife Obesity and Its Metabolic Consequences, Cerebrovascular Disease, and Cognitive Decline. *J Clin Endocrinol Metab* **106**, e4260-e4274, doi:10.1210/clinem/dgab135 (2021).

35 Rhea, E. M. *et al.* Blood-Brain Barriers in Obesity. *AAPS J* **19**, 921-930, doi:10.1208/s12248-017-0079-3 (2017).

36 Collignon, A., Dion-Albert, L., Menard, C. & Coelho-Santos, V. Sex, hormones and cerebrovascular function: from development to disorder. *Fluids Barriers CNS* **21**, 2, doi:10.1186/s12987-023-00496-3 (2024).

37 Aanerud, J., Borghammer, P., Rodell, A., Jonsdottir, K. Y. & Gjedde, A. Sex differences of human cortical blood flow and energy metabolism. *J Cereb Blood Flow Metab* **37**, 2433-2440, doi:10.1177/0271678X16668536 (2017).

38 Koep, J. L. *et al.* Sex modifies the relationship between age and neurovascular coupling in healthy adults. *J Cereb Blood Flow Metab* **43**, 1254-1266, doi:10.1177/0271678X231167753 (2023).

39 Moon, Y., Lim, C., Kim, Y. & Moon, W. J. Sex-Related Differences in Regional Blood-Brain Barrier Integrity in Non-Demented Elderly Subjects. *Int J Mol Sci* **22**, doi:10.3390/ijms22062860 (2021).

40 Bianco, A., Antonacci, Y. & Liguori, M. Sex and Gender Differences in Neurodegenerative Diseases: Challenges for Therapeutic Opportunities. *Int J Mol Sci* **24**, doi:10.3390/ijms24076354 (2023).

41 Abi-Ghanem, C., Robison, L. S. & Zuloaga, K. L. Androgens' effects on cerebrovascular function in health and disease. *Biol Sex Differ* **11**, 35, doi:10.1186/s13293-020-00309-4 (2020).

42 Robison, L. S., Gannon, O. J., Salinero, A. E. & Zuloaga, K. L. Contributions of sex to cerebrovascular function and pathology. *Brain Res* **1710**, 43-60, doi:10.1016/j.brainres.2018.12.030 (2019).

43 Kris-Etherton, P. M. *et al.* Strategies for Promotion of a Healthy Lifestyle in Clinical Settings: Pillars of Ideal Cardiovascular Health: A Science Advisory From the American Heart Association. *Circulation* **144**, e495-e514, doi:10.1161/CIR.0000000000001018 (2021).

44 Wadden, T. A., Tronieri, J. S. & Butryn, M. L. Lifestyle modification approaches for the treatment of obesity in adults. *Am Psychol* **75**, 235-251, doi:10.1037/amp0000517 (2020).

45 Cavalcanti-de-Albuquerque, J. P. & Donato, J., Jr. Rolling out physical exercise and energy homeostasis: Focus on hypothalamic circuitries. *Front Neuroendocrinol* **63**, 100944, doi:10.1016/j.yfrne.2021.100944 (2021).

46 Hofer, S. J., Carmona-Gutierrez, D., Mueller, M. I. & Madeo, F. The ups and downs of caloric restriction and fasting: from molecular effects to clinical application. *EMBO Mol Med* **14**, e14418, doi:10.15252/emmm.202114418 (2022).

47 Tsurugizawa, T., Djemai, B. & Zalesky, A. The impact of fasting on resting state brain networks in mice. *Sci Rep* **9**, 2976, doi:10.1038/s41598-019-39851-6 (2019).

48 de Cabo, R. & Mattson, M. P. Effects of Intermittent Fasting on Health, Aging, and Disease. *N Engl J Med* **381**, 2541-2551, doi:10.1056/NEJMra1905136 (2019).

49 Harder-Lauridsen, N. M. *et al.* Ramadan model of intermittent fasting for 28 d had no major effect on body composition, glucose metabolism, or cognitive functions in healthy lean men. *Nutrition* **37**, 92-103, doi:10.1016/j.nut.2016.12.015 (2017).

50 Currenti, W. *et al.* Association between Time Restricted Feeding and Cognitive Status in Older Italian Adults. *Nutrients* **13**, doi:10.3390/nu13010191 (2021).

51 Sutton, E. F. *et al.* Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* **27**, 1212-1221 e1213, doi:10.1016/j.cmet.2018.04.010 (2018).

52 Ooi, T. C. *et al.* Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic changes: A 3-Year Progressive Study. *Nutrients* **12**, doi:10.3390/nu12092644 (2020).

53 Baik, S. H., Rajeev, V., Fann, D. Y., Jo, D. G. & Arumugam, T. V. Intermittent fasting increases adult hippocampal neurogenesis. *Brain Behav* **10**, e01444, doi:10.1002/brb3.1444 (2020).

54 Bang, E., Fincher, A. S., Nader, S., Murchison, D. A. & Griffith, W. H. Late-Onset, Short-Term Intermittent Fasting Reverses Age-Related Changes in Calcium Buffering and Inhibitory Synaptic Transmission in Mouse Basal Forebrain Neurons. *J Neurosci* **42**, 1020-1034, doi:10.1523/JNEUROSCI.1442-21.2021 (2022).

55 Rajeev, V. *et al.* Intermittent Fasting Attenuates Hallmark Vascular and Neuronal Pathologies in a Mouse Model of Vascular Cognitive Impairment. *Int J Biol Sci* **18**, 6052-6067, doi:10.7150/ijbs.75188 (2022).

56 Liu, Z. *et al.* Long-term intermittent fasting improves neurological function by promoting angiogenesis after cerebral ischemia via growth differentiation factor 11 signaling activation. *PLoS One* **18**, e0282338, doi:10.1371/journal.pone.0282338 (2023).

57 Andika, F. R., Yoon, J. H., Kim, G. S. & Jeong, Y. Intermittent Fasting Alleviates Cognitive Impairments and Hippocampal Neuronal Loss but Enhances Astrocytosis in Mice with Subcortical Vascular Dementia. *J Nutr* **151**, 722-730, doi:10.1093/jn/nxaa384 (2021).

58 Wang, R. *et al.* Caloric restriction ameliorates high-fat diet induced cognitive deficits through attenuating neuroinflammation via the TREM2-PI3K/AKT signaling pathway. *Food Funct* **12**, 6464-6478, doi:10.1039/d0fo02946g (2021).

59 Leclerc, E. *et al.* The effect of caloric restriction on working memory in healthy non-obese adults. *CNS Spectr* **25**, 2-8, doi:10.1017/S1092852918001566 (2020).

60 Prehn, K. *et al.* Caloric Restriction in Older Adults-Differential Effects of Weight Loss and Reduced Weight on Brain Structure and Function. *Cereb Cortex* **27**, 1765-1778, doi:10.1093/cercor/bhw008 (2017).

61 Rahmani, F. *et al.* 12-weeks of caloric restriction diet improves cortical cerebral blood flow in healthy middle-age adults. *Alzheimer's & Dementia* **19**, e060865, doi:<https://doi.org/10.1002/alz.060865> (2023).

62 Parikh, I. *et al.* Caloric restriction preserves memory and reduces anxiety of aging mice with early enhancement of neurovascular functions. *Aging (Albany NY)* **8**, 2814-2826, doi:10.18632/aging.101094 (2016).

63 Tropea, T. & Mandala, M. Caloric restriction enhances vascular tone of cerebral and mesenteric resistance arteries in aged rats. *Mech Ageing Dev* **197**, 111520, doi:10.1016/j.mad.2021.111520 (2021).

64 Kim, H. *et al.* Caloric restriction improves diabetes-induced cognitive deficits by attenuating neurogranin-associated calcium signaling in high-fat diet-fed mice. *J Cereb Blood Flow Metab* **36**, 1098-1110, doi:10.1177/0271678X15606724 (2016).

65 La Russa, D., Marrone, A., Mandala, M., Macirella, R. & Pellegrino, D. Antioxidant/Anti-Inflammatory Effects of Caloric Restriction in an Aged and Obese Rat Model: The Role of Adiponectin. *Biomedicines* **8**, doi:10.3390/biomedicines8120532 (2020).

66 Opatrilova, R. *et al.* Adipokines in neurovascular diseases. *Biomed Pharmacother* **98**, 424-432, doi:10.1016/j.biopha.2017.12.074 (2018).

67 Tu, Y. F., Lu, P. J., Huang, C. C., Ho, C. J. & Chou, Y. P. Moderate dietary restriction reduces p53-mediated neurovascular damage and microglia activation after hypoxic ischemia in neonatal brain. *Stroke* **43**, 491-498, doi:10.1161/STROKEAHA.111.629931 (2012).

68 Zhang, J. *et al.* Preconditioning with partial caloric restriction confers long-term protection against grey and white matter injury after transient focal ischemia. *J Cereb Blood Flow Metab* **39**, 1394-1409, doi:10.1177/0271678X18785480 (2019).

69 Ciobanu, O. *et al.* Caloric restriction stabilizes body weight and accelerates behavioral recovery in aged rats after focal ischemia. *Aging Cell* **16**, 1394-1403, doi:10.1111/acel.12678 (2017).

70 Huang, J. T. *et al.* Calorie restriction conferred improvement effect on long-term rehabilitation of ischemic stroke via gut microbiota. *Pharmacol Res* **170**, 105726, doi:10.1016/j.phrs.2021.105726 (2021).

71 de Carvalho, T. S. *et al.* Hypocaloric Diet Initiated Post-Ischemia Provides Long-Term Neuroprotection and Promotes Peri-Infarct Brain Remodeling by Regulating Metabolic and Survival-Promoting Proteins. *Mol Neurobiol* **58**, 1491-1503, doi:10.1007/s12035-020-02207-7 (2021).

72 Kim, C. *et al.* Energy Restriction Enhances Adult Hippocampal Neurogenesis-Associated Memory after Four Weeks in an Adult Human Population with Central Obesity; a Randomized Controlled Trial. *Nutrients* **12**, doi:10.3390/nu12030638 (2020).

73 Teong, X. T. *et al.* Eight weeks of intermittent fasting versus calorie restriction does not alter eating behaviors, mood, sleep quality, quality of life and cognitive performance in women with overweight. *Nutr Res* **92**, 32-39, doi:10.1016/j.nutres.2021.06.006 (2021).

74 Horie, N. C. *et al.* Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals With Mild Cognitive Impairment. *J Clin Endocrinol Metab* **101**, 1104-1112, doi:10.1210/jc.2015-2315 (2016).

75 Stillman, C. M. *et al.* Changes in cerebral perfusion following a 12-month exercise and diet intervention. *Psychophysiology* **58**, e13589, doi:10.1111/psyp.13589 (2021).

76 Loffler, M. C. *et al.* Challenges in tackling energy expenditure as obesity therapy: From preclinical models to clinical application. *Mol Metab* **51**, 101237, doi:10.1016/j.molmet.2021.101237 (2021).

77 Soares, M. J. & Muller, M. J. Resting energy expenditure and body composition: critical aspects for clinical nutrition. *Eur J Clin Nutr* **72**, 1208-1214, doi:10.1038/s41430-018-0220-0 (2018).

78 Talbot, J. S. *et al.* Neurovascular coupling and cerebrovascular hemodynamics are modified by exercise training status at different stages of maturation during youth. *Am J Physiol Heart Circ Physiol* **325**, H510-H521, doi:10.1152/ajpheart.00302.2023 (2023).

79 Park, J. H., Moon, J. H., Kim, H. J., Kong, M. H. & Oh, Y. H. Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks. *Korean J Fam Med* **41**, 365-373, doi:10.4082/kjfm.20.0165 (2020).

80 Qiu, Y. *et al.* Exercise sustains the hallmarks of health. *J Sport Health Sci* **12**, 8-35, doi:10.1016/j.jshs.2022.10.003 (2023).

81 Thyfault, J. P. & Bergouignan, A. Exercise and metabolic health: beyond skeletal muscle. *Diabetologia* **63**, 1464-1474, doi:10.1007/s00125-020-05177-6 (2020).

82 Di Liegro, C. M., Schiera, G., Proia, P. & Di Liegro, I. Physical Activity and Brain Health. *Genes (Basel)* **10**, doi:10.3390/genes10090720 (2019).

83 Guadagni, V. *et al.* Aerobic exercise improves cognition and cerebrovascular regulation in older adults. *Neurology* **94**, e2245-e2257, doi:10.1212/WNL.0000000000009478 (2020).

84 Harvey, S. B. *et al.* Exercise and the Prevention of Depression: Results of the HUNT Cohort Study. *Am J Psychiatry* **175**, 28-36, doi:10.1176/appi.ajp.2017.16111223 (2018).

85 Mendez Colmenares, A. *et al.* White matter plasticity in healthy older adults: The effects of aerobic exercise. *Neuroimage* **239**, 118305, doi:10.1016/j.neuroimage.2021.118305 (2021).

86 Broadhouse, K. M. *et al.* Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. *Neuroimage Clin* **25**, 102182, doi:10.1016/j.nicl.2020.102182 (2020).

87 Bilek, F., Cetisli-Korkmaz, N., Ercan, Z., Deniz, G. & Demir, C. F. Aerobic exercise increases irisin serum levels and improves depression and fatigue in patients with relapsing remitting multiple sclerosis: A randomized controlled trial. *Mult Scler Relat Disord* **61**, 103742, doi:10.1016/j.msard.2022.103742 (2022).

88 Maurus, I. *et al.* Exercise as an add-on treatment in individuals with schizophrenia: Results from a large multicenter randomized controlled trial. *Psychiatry Res* **328**, 115480, doi:10.1016/j.psychres.2023.115480 (2023).

89 Jia, R. X., Liang, J. H., Xu, Y. & Wang, Y. Q. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr* **19**, 181, doi:10.1186/s12877-019-1175-2 (2019).

90 Sleiman, S. F. *et al.* Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. *Elife* **5**, doi:10.7554/eLife.15092 (2016).

91 Nilsson, J. *et al.* Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. *Sci Rep* **10**, 4395, doi:10.1038/s41598-020-60124-0 (2020).

92 Kullmann, S. *et al.* Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. *JCI Insight* **7**, doi:10.1172/jci.insight.161498 (2022).

93 Nijssen, K. M. R., Mensink, R. P. & Joris, P. J. Effects of Intranasal Insulin Administration on Cerebral Blood Flow and Cognitive Performance in Adults: A Systematic Review of Randomized, Placebo-Controlled Intervention Studies. *Neuroendocrinology* **113**, 1-13, doi:10.1159/000526717 (2023).

94 Swain, R. A. *et al.* Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience* **117**, 1037-1046, doi:10.1016/s0306-4522(02)00664-4 (2003).

95 Graham, L. C. *et al.* Exercise prevents obesity-induced cognitive decline and white matter damage in mice. *Neurobiol Aging* **80**, 154-172, doi:10.1016/j.neurobiolaging.2019.03.018 (2019).

96 Bailey, D. M. *et al.* Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. *Stroke* **44**, 3235-3238, doi:10.1161/STROKEAHA.113.002589 (2013).

97 Thomas, B. P. *et al.* Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2. *J Magn Reson Imaging* **38**, 1177-1183, doi:10.1002/jmri.24090 (2013).

98 Murrell, C. J. *et al.* Cerebral blood flow and cerebrovascular reactivity at rest and during sub-maximal exercise: effect of age and 12-week exercise training. *Age (Dordr)* **35**, 905-920, doi:10.1007/s11357-012-9414-x (2013).

99 Espeland, M. A. *et al.* Long Term Effect of Intensive Lifestyle Intervention on Cerebral Blood Flow. *J Am Geriatr Soc* **66**, 120-126, doi:10.1111/jgs.15159 (2018).

100 Renaudin, N. *et al.* Functional ultrasound localization microscopy reveals brain-wide neurovascular activity on a microscopic scale. *Nat Methods* **19**, 1004-1012, doi:10.1038/s41592-022-01549-5 (2022).

101 Williams, C. G., Lee, H. J., Asatsuma, T., Vento-Tormo, R. & Haque, A. An introduction to spatial transcriptomics for biomedical research. *Genome Med* **14**, 68, doi:10.1186/s13073-022-01075-1 (2022).

102 Avraham, Y. *et al.* Leptin induces neuroprotection neurogenesis and angiogenesis after stroke. *Curr Neurovasc Res* **8**, 313-322, doi:10.2174/156720211798120954 (2011).

103 Cui, Q. *et al.* Leptin Promotes Angiogenesis via Pericyte STAT3 Pathway upon Intracerebral Hemorrhage. *Cells* **11**, doi:10.3390/cells11172755 (2022).

104 Fernandez, A. M. *et al.* Insulin regulates neurovascular coupling through astrocytes. *Proc Natl Acad Sci U S A* **119**, e2204527119, doi:10.1073/pnas.2204527119 (2022).

105 Kondo, T. *et al.* Knockout of insulin and IGF-1 receptors on vascular endothelial cells protects against retinal neovascularization. *J Clin Invest* **111**, 1835-1842, doi:10.1172/JCI17455 (2003).

106 Warmke, N. *et al.* Pericyte Insulin Receptors Modulate Retinal Vascular Remodeling and Endothelial Angiopoietin Signaling. *Endocrinology* **162**, doi:10.1210/endocr/bqab182 (2021).

107 Hauptmann, J. *et al.* Interleukin-1 promotes autoimmune neuroinflammation by suppressing endothelial heme oxygenase-1 at the blood-brain barrier. *Acta Neuropathol* **140**, 549-567, doi:10.1007/s00401-020-02187-x (2020).

108 Chen, A. Q. *et al.* Microglia-derived TNF-alpha mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. *Cell Death Dis* **10**, 487, doi:10.1038/s41419-019-1716-9 (2019).

109 Spranger, J. *et al.* Adiponectin does not cross the blood-brain barrier but modifies cytokine expression of brain endothelial cells. *Diabetes* **55**, 141-147 (2006).

110 Bloemer, J. *et al.* Role of Adiponectin in Central Nervous System Disorders. *Neural Plast* **2018**, 4593530, doi:10.1155/2018/4593530 (2018).

111 Svart, M. *et al.* Regional cerebral effects of ketone body infusion with 3-hydroxybutyrate in humans: Reduced glucose uptake, unchanged oxygen consumption and increased blood flow by positron emission tomography. A randomized, controlled trial. *PLoS One* **13**, e0190556, doi:10.1371/journal.pone.0190556 (2018).

112 Hasselbalch, S. G. *et al.* Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am J Physiol* **270**, E746-751, doi:10.1152/ajpendo.1996.270.5.E746 (1996).

113 Ma, D. *et al.* Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Sci Rep* **8**, 6670, doi:10.1038/s41598-018-25190-5 (2018).

114 van Hall, G. *et al.* Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab* **29**, 1121-1129, doi:10.1038/jcbfm.2009.35 (2009).

115 Ide, K., Schmalbruch, I. K., Quistorff, B., Horn, A. & Secher, N. H. Lactate, glucose and O2 uptake in human brain during recovery from maximal exercise. *J Physiol* **522 Pt 1**, 159-164, doi:10.1111/j.1469-7793.2000.t01-2-00159.xm (2000).

116 Maran, A., Cranston, I., Lomas, J., Macdonald, I. & Amiel, S. A. Protection by lactate of cerebral function during hypoglycaemia. *Lancet* **343**, 16-20, doi:10.1016/s0140-6736(94)90876-1 (1994).

117 Takechi, R., Pallebage-Gamarallage, M. M., Lam, V., Giles, C. & Mamo, J. C. Aging-related changes in blood-brain barrier integrity and the effect of dietary fat. *Neurodegener Dis* **12**, 125-135, doi:10.1159/000343211 (2013).

118 Shaheryar, Z. A. *et al.* Natural Fatty Acid Guards against Brain Endothelial Cell Death and Microvascular Pathology following Ischemic Insult in the Presence of Acute Hyperglycemia. *Biomedicines* **11**, doi:10.3390/biomedicines11123342 (2023).

119 Sung, K. S. *et al.* Saturated Fatty Acid Emulsions Open the Blood-Brain Barrier and Promote Drug Delivery in Rat Brains. *Pharmaceutics* **16**, doi:10.3390/pharmaceutics16020246 (2024).

120 Milanski, M. *et al.* Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J Neurosci* **29**, 359-370, doi:10.1523/JNEUROSCI.2760-08.2009 (2009).