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Perspective

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The interactions between energy homeostasis and neurovascular plasticity

Bandy Chen[1] ✉, Elisa de Launoit[2], David Meseguer[1], Cristina Garcia Caceres[3,4], Anne Eichmann[1,5,6], Nicolas Renier[2] & Marc Schneeberger[1,7] ✉

Abstract

Food intake and energy expenditure are sensed and processed by multiple brain centres to uphold energy homeostasis. Evidence from the past decade points to the brain vasculature as a new critical player in regulating energy balance that functions in close association with the local neuronal networks. Nutritional imbalances alter many properties of the neurovascular system (such as neurovascular coupling and blood–brain barrier permeability), thus suggesting a bidirectional link between the nutritional milieu and neurovascular health. Increasing numbers of people are consuming a Western diet (comprising ultra-processed food with high-fat and high-sugar content) and have a sedentary lifestyle, with these factors contributing to the current obesity epidemic. Emerging pharmacological interventions (for example, glucagon-like peptide 1 receptor agonists) successfully trigger weight loss. However, whether these approaches can reverse the detrimental effects of long-term exposure to the Western diet (such as neurovascular uncoupling, neuroinflammation and blood–brain barrier disruption) and maintain stable body weight in the long-term needs to be clarified in addition to possible adverse effects. Lifestyle interventions revert the nutritional trigger for obesity and positively affect our overall health, including the cardiovascular system. This Perspective examines how lifestyle interventions affect the neurovascular system and neuronal networks.

Sections

[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, Paris, France. [7]Wu Tsai Institute for Mind and Brain, Yale University, New Haven, CT, USA. ✉e-mail: bandy.chen@yale.edu; marc.schneebergerpane@yale.edu

Introduction

A dynamic interplay occurs between the brain and body to maintain energy balance, driven by complex and redundant neuronal circuits and ensuring survival[1]. These circuits sense and integrate signals from the body, modulating internal homeostasis and driving appropriate responses. Key to this communication are circulating factors (that is, nutrients, hormones and metabolites) conveyed by the bloodstream[2], alongside direct neural inputs from the peripheral nervous system[3]. 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 during embryonic development as cerebral endothelial cells mature[5]. This maturation process selectively restricts trafficking routes through the endothelium while maintaining specific transport mechanisms. The barrier that forms 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, which further controls and restricts the routes available to molecules from the bloodstream to neural cells. The composition of the NVU, which varies across brain regions and over time[7], has a pivotal role in determining how brain circuits sense circulating factors. Therefore, alterations in the molecular and cellular composition of the BBB could profoundly affect the responses of the brain 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 in the bloodstream. First, the local cerebral blood flow, which adapts in response to neuronal activity and metabolic demands, ensures an adequate nutrient supply and waste removal through neurovascular coupling (communication between the different cell types of the NVU)[8]. Alterations to cerebral blood flow have often been documented in pathological conditions and could affect circuit functions by compromising neurovascular coupling[6]. Second, the structure and density of the cerebral vascular network vary notably across brain regions, with brain nuclei involved in energy homeostasis often exhibiting high vascularization densities in rodents[9,10]. This observation suggests that vascular density might be fundamental for modulating the function and activity of neurons confined in brain regions responsible for nutrient sensing. Of note, this hypothesis has yet to be explored. Metabolic shifts, such as overnutrition, are linked to various cerebral alterations such as BBB permeability, neurovascular uncoupling, demyelination and glymphatic dysfunction; therefore, clarifying the crosstalk between energy homeostasis and neurovascular plasticity could help elucidate the mechanisms that link obesity with its central comorbidities. Developing novel techniques to explore neurovascular plasticity have rendered this long-standing and formidable task achievable (Box 1).

This Perspective contrasts work from the past decade to emphasize the need to exploit the link between neurovascular interfaces and energy homeostasis in health and disease. We outline how these underexplored mechanisms are rewired in metabolic shifts, such as obesity, intermittent fasting, caloric restriction and physical activity, to understand the crosstalk between energy homeostasis and neurovascular plasticity. Thus, we shed 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

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 blood vessels and neurons, have been identified to have a major role in modulating neurovascular plasticity to control food intake: tanycytes and astrocytes.

Control of energy intake under healthy conditions

The arcuate nucleus of the hypothalamus (ARH) is the major hub in the central nervous system that controls energy homeostasis[11]. The privileged location of the ARH at the midline of the ventral hypothalamus positions it at a strategic nexus to sense circulating nutrients. Importantly, the ARH is located between the median eminence (a circumventricular organ containing fenestrated capillaries) and the third ventricle, which enables 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 CSF[12]. In mice, low glucose levels in the bloodstream increase the permeability of this barrier via the expression of tanycytic vascular endothelial growth factor A (VEGFA)[13]. In addition, the specific ablation of tanycytes in this region induces obesity in male mice[14]. Interestingly, the permeability of the fenestrated capillaries in the mouse median eminence can also be directly modulated by distant melanin-concentrating hormone neurons of the lateral hypothalamic area, which are capable of producing VEGFA[15]. This observation 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 for innovative therapeutic strategies 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 complete coverage of almost all cerebral capillaries[16]. 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 control[10,17]. The close association of astrocytes with vascular beds in the mediobasal part of the hypothalamus renders them particularly susceptible to peripheral metabolic changes under physiological conditions or during obesity[10] (Fig. 1). This influence fosters cellular adaptations that are 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 way[10,18].

Another important way in which neural cells can control nutrient sensing from the bloodstream is by modulating cerebral blood flow via neurovascular coupling. When neural activity locally increases in response to nutrient sensing or humoral fluctuations, cerebral blood flow in the active regions is enhanced[19]. Increased blood flow is generally thought of as 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 neurovascular coupling responds to nutrient sensing and other cues related to energy intake, we might uncover alternative mechanisms participating in appetite regulation.

Alterations during obesity

Chronic overnutrition leading to obesity affects the functions of astrocytes in a multifaceted and remarkably diverse manner. Owing to their

Box 1 | Advances in the study of neurovascular plasticity

The vasculature of the brain comprises a complex network of arteries, capillaries and veins that span various scales, from millimetre-sized to micrometre-sized vessels. This complexity has historically posed challenges in quantifying structural changes in cerebrovascular topology across the brain. However, work from the past decade and breakthroughs in technology have revolutionized our ability to visualize and quantify vascular plasticity at molecular, anatomical and functional levels, thereby offering unprecedented insights into neurovascular dynamics. Volumetric and intravital imaging together with spatial transcriptomics have emerged as complementary tools to identify the spatiotemporal dynamics of the cerebral landscape.

Immunolabelling-based tissue clearing (such as iDISCO+) combined with 3D light-sheet microscopy, enables the generation of high-resolution maps that detail vessel tortuosity, length and interruptions[9]. By referencing the Allen Brain Atlas, researchers can precisely identify regions of interest that exhibit hypervascularization or hypovascularization events.

Intravital imaging techniques, including functional ultrasound, have transformed our ability to capture dynamic microvasculature changes in response to brain activation with high spatiotemporal resolution[121]. Unlike traditional functional MRI, functional ultrasound provides superior spatiotemporal resolution, which is crucial for localizing vessel remodelling events.

Another advance lies in studying the molecular importance of neurovascular topological events within the neurovascular unit, where neuronal, vascular and immune structures converge. Single-cell RNA sequencing 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 remodelled brain regions requires a spatial component. Spatial transcriptomics (such as the Visium platform) reveal the spatial organization of cell types and their molecular connectivity within the brain[122].

Together, these advances offer a comprehensive approach to the study of 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.

importance in the makeup of the NVU, astrocytes could be one of the prime suspects that link obesity to cognitive impairments[20] through the disruption of vascular integrity and permeability. For instance, in mouse models of diet-induced obesity and in humans with obesity, elevated leptin levels in the circulation have been shown to trigger the release of soluble factors such as astrocytic-derived VEGF, which leads to alterations in the integrity and permeability of vascular beds and angiogenesis at the level of the microvasculature[10,18]. This change increases the leakiness of the parenchymal barrier to both the humoral and CSF circulation. Moreover, the loss of insulin receptors in astrocytes in mice leads to reduced expression of glucose transporter 1 (GLUT1), resulting in restricted delivery of glucose into the brain[21,22]. Similarly, a hypercaloric diet in mice induces transient alterations in brain glucose uptake by modulating GLUT1 expression on vascular endothelial cells[23]. These studies propose that the effect of glial cell-derived VEGF is crucial for sustaining brain glucose uptake; improving glucose uptake by favouring high VEGF expression can alleviate cognitive impairments associated with obesity[23].

Obesity-induced changes in cerebral blood flow can partly explain how chronic overnutrition interferes with nutrient sensing in the brain, an effect that persists even after weight loss[24]. Indeed, in middle-aged and older adults, an increase in BMI was associated with decreased hippocampal cerebral blood flow and cerebrovascular reactivity, which is the capacity of the brain's vasculature to alter cerebral blood flow in response to a stimulus[25,26]. The effect of obesity on cerebral blood flow is more potent than that of ageing, with an increase in waist circumference of 1.3 cm in older adults linked to the same reduction in cerebral blood flow as a 1-year increase in age[27].

Plastic changes to neurovascular coupling during nutrient shifts have been extensively studied in preclinical models. High blood levels of glucose have been found to affect both neurovascular coupling and cerebrovascular patterning due to alterations in BBB integrity[28]. Hyperglycaemia-induced neuronal activity leads to elevated cerebral blood flow as a compensatory mechanism. However, this prolonged effect can trigger a negative feedback mechanism, which impairs nutrient sensing, neuronal activity and neurovascular coupling[29]. Feeding mice a high-fat diet (HFD) for 8 weeks reduces their increase in blood flow in response to neuronal stimulation (that is, functional hyperaemia) via whisker stimulation, which suggests a reduction in the strength of cortical neurovascular coupling early after a dietary shift[30]. These findings suggest that metabolic abnormalities associated with a HFD occur earlier in the brain compared with the periphery. In rats, feeding with a cafeteria diet (consisting of grocery store-purchased highly processed food items) over a short period of 12–16 weeks increases resting cerebral blood flow in the hippocampus and reduces cerebrovascular reactivity. This change occurred without affecting learning and memory[31,32]. However, memory deficits were seen in rats after a long-term cafeteria diet (30 weeks)[31,32]. These variations can be attributed to the duration of the cafeteria diet, leading to different levels of metabolic dysfunction. Neither the short-term or long-term cafeteria diet led to changes in the density of CA1 neurons (involved in memory formation and retrieval), structural vascular alterations, nor altered cerebrovascular integrity, which suggests that changes in cerebral blood flow and volume are more functional than structural. Determining in such models whether changes to the cerebral blood flow are solely linked to a shift in the plasma concentration of nutrients or signalling factors will be important, as will investigating if chronic changes to neural activity levels in specific regions also has a direct role.

Investigating the onset and duration of obesity in relation to neurovascular coupling and cerebrovascular rewiring will provide a timeline to understand the adaptations of the brain to overnutrition. Moreover, the effect of obesity on cerebral blood flow goes beyond nutrient sensing as metabolic abnormalities, such as insulin and leptin resistance, chronic inflammation and hypertension contribute to a heightened risk of ischaemic stroke[33] or silent brain infarcts[34]. Increased adiposity in midlife is also associated with small vessel disease, leading to changes in white matter that affect both subcortical and cortical regions and result in cognitive deficits[35]. In summary, obesity substantially affects

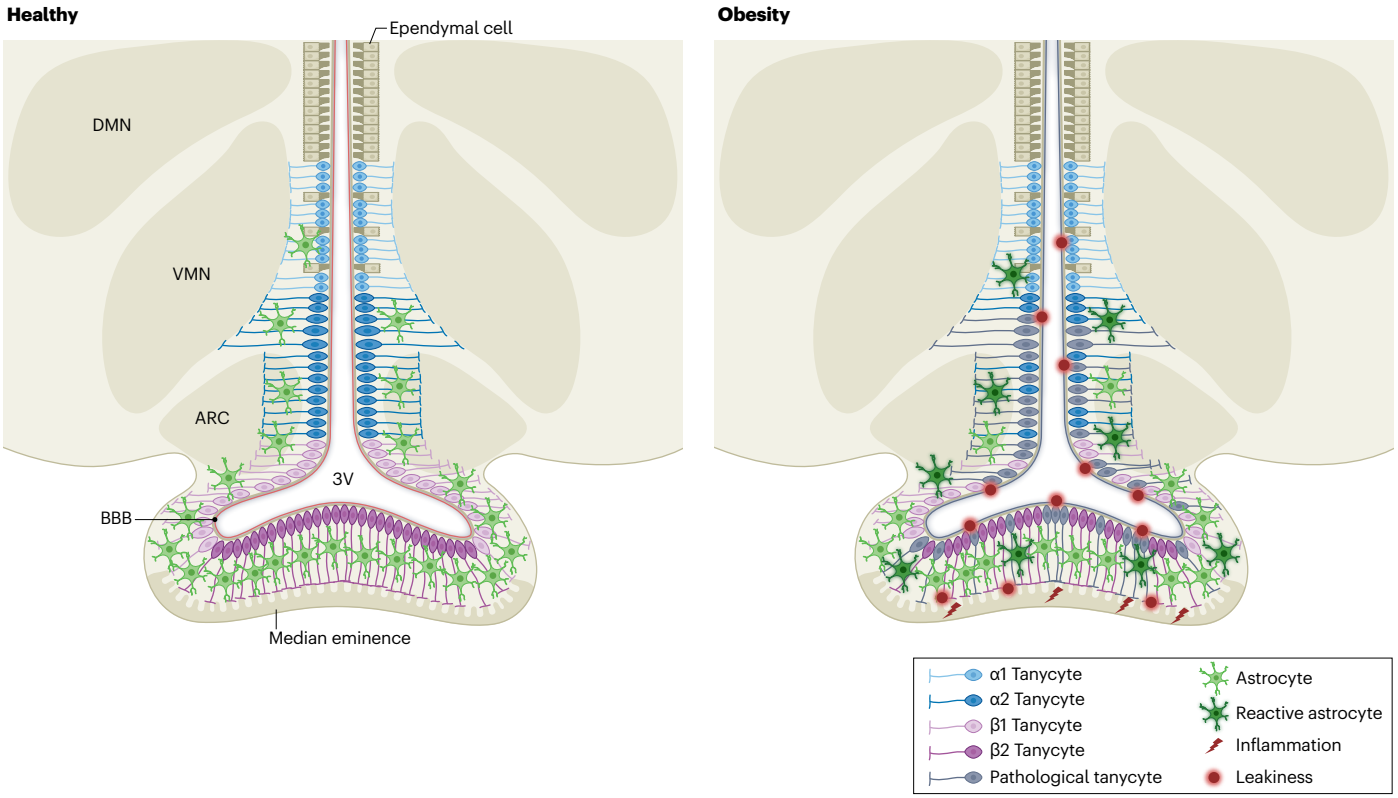

Fig. 1 | Pathological rewiring of the neurovascular landscape of the hypothalamus. Left panel: the structure of the neurovascular unit in healthy conditions. Right panel: during obesity, chronic overnutrition leads to excessive neuroinflammation to compensate for the continuous metabolic turnover. Pathological levels of glial activity increase blood–brain barrier (BBB) permeability and infiltration of peripheral immune cells, resulting in a vicious cycle of neurovascular uncoupling. Tanycytes lining up the ventricle become leaky (pathological tanycytes) and there is an altered inflow of cerebral spinal fluid to the parenchyma. As a result, impaired communication between the neurovascular unit leads to an imbalance between afferent and efferent signals and overall energy dyshomeostasis. 3V, third ventricle; ARC, arcuate nucleus; DMN, dorsomedial hypothalamic nucleus; VMN, ventromedial nucleus of hypothalamus.

the vascular system of the brain, which disrupts 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 health[36].

Sexual dimorphism in the neurovasculature

Sex differences exert a notable influence on the development and progression of the neurovascular landscape[37]. In cortical regions, young women demonstrate higher cerebral blood flow than young men in the frontal and parietal lobes; however, these differences shrink after age 65 years, indicating a greater age-related decline in cerebral blood flow for women[38,39]. On the other hand, the age-related decline in BBB function of cortical regions is found to be larger in men[40]. From epidemiological studies, sexual dysmorphisms are seen in the prevalence of metabolic and neurological disorders[41]. For example, men are at a greater risk than women for vascular complications associated with cognitive impairment and dementia[42].

The discrepancies in the neurovascular landscape and susceptibility to neurological disorders in men and women can be explained by the difference in hormonal and metabolic profiles. Both oestrogen and androgens promote angiogenesis and cerebrovascular remodelling[43]. Oestrogen decreases cerebral vascular tone and increases cerebral blood flow, whereas androgens increase cerebral vascular tone and decrease cerebral blood flow. The difference in body composition and hormonal profile between sexes contributes 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 effect of sex differences and pathological states (states of varied metabolic profile) on the neurovascular landscape.

The effect of lifestyle interventions

Lifestyle interventions include a range of activities aimed at enhancing overall quality of life and reducing the risk of various chronic diseases[44]. Some of the most effective lifestyle interventions for managing metabolic and neurological risk factors (such as BMI or blood pressure) involve intermittent fasting, caloric restriction and physical activity[45]. The beneficial effects of intermittent fasting, caloric restriction and physical activity on peripheral and central metabolism have been extensively reviewed[46,47]. Here, instead, we 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 effect on neuronal activity and vasomotricity, which is visible at the level of whole-brain functional connectivity and regional cerebral blood flow[48]. High-field functional MRI studies reveal specific patterns of functional connectivity during fasting, particularly in the hippocampus–cortex pathway, which might reinforce our urge for food[48]. Intermittent fasting has gained attention in recent years for its potential in weight management and treating metabolic disorders. Multiple types of intermittent fasting programmes have been developed, with the most popular two being alternate-day fasting and time-restricted eating[49]. For alternate-day fasting, individuals fast on alternate days and consume under 500 kcal on a fasting day, while time-restricted eating requires individuals to fast for a certain period daily such as the 16:8 fasting (16 h of fasting window and 8 h of eating window). During fasting, the main fuel source utilized by cells switches from glucose to ketone bodies, and such periodic metabolic switching is an evolutionarily conserved response that enhances metabolism and reduces inflammation[50]. While its effects on metabolic and cognitive functions in healthy, lean individuals are fairly modest[51], the benefits of intermittent fasting in older adults and pathological states are considerable[50]. For instance, a shortened eating window in older adults (aged >65 years) has shown promise in reducing the risk of age-associated cognitive impairment[52]. Furthermore, early time-restricted eating (6-h eating period, with dinner before 3 p.m.) in individuals with prediabetes substantially improves various metabolic parameters, including circulating insulin levels and insulin sensitivity, blood pressure and oxidative stress[53]. Among older adults with mild cognitive impairment, intermittent fasting on Monday and Thursday every week beginning from sunrise to sunset over 36 months notably enhanced cognitive performance[54]. In sum, the neuroprotective role of intermittent fasting in humans is evident.

In young mice, 3 months of intermittent fasting (12 h, 16 h or 24 h of food deprivation on a daily basis; fasting was daily in the 12-h and 16-h groups and every other day in the 24-h group) yields remarkable effects on hippocampal neurogenesis and long-term potentiation of hippocampal synapses[55]. In aged mice, alternate-day fasting for 6 weeks reverses age-related synaptic changes in Ca^{2+} buffering and inhibitory transmission in dissociated neurons, albeit without mitigating cognitive impairments in vivo[56]. Beyond these limited neurophysiological

Table 1 | Circulating factors and their effects on the NVU

Factor	Main sources	Major effect on the NVU
Leptin	Adipose tissue	Promotes angiogenesis and vascular remodelling in a region-specific manner in mice[10] Regulates astrocytic release of soluble factors, such as vascular endothelial growth factor, to modulate BBB function and properties in mice[10] Promotes neurogenesis and angiogenesis after stroke[102], and angiogenesis via the pericyte STAT3 pathway upon intracerebral haemorrhage in mice[103]
Insulin	Pancreas	Modulates angiogenesis in the cortex via astrocytes in young but not in aged mice[104] Regulates neurovascular coupling: glucose uptake handling couples with blood flow via astrocytes in mice[22,104] Both insulin and IGF1 signalling in endothelium have a role in the proliferation of retinal endothelial cells through the expression of vascular mediators in mice[105] Pericyte insulin receptors modulate retinal vascular remodelling (vascular sprouting) and endothelial angiopoietin signalling to promote venous plexus development in mice[106]
Cytokines (for example, IL-1β, IL-6, TNF)	Immune cells, macrophages, glial cells	Regulates the integrity and permeability of the BBB in mice[107] Vascular remodelling Enhances glia reactivity and local immune cell recruitment Elevated levels promote inflammation, which leads to BBB disruption in rats[108]
Adiponectin	Adipose tissue	Does not cross the BBB Adiponectin receptors on brain endothelial cells modulate cytokine secretion in mice[109] Potential cerebroprotective action against central nervous system pathologies (for example, stroke) via receptor-mediated mechanisms[110]
Ketone bodies (for example, BHB)	Liver	Intravenous infusion of BHB: regulates glucose transport across the BBB, which leads to decreases in cerebral glucose consumption and increases blood flow in humans[111,112] Ketogenic diet enhances neurovascular functions: elevates cerebral blood flow, particularly in the ventromedial hypothalamus in mice[113]
Lactate	Muscle cells, red blood cells, glial cells	Exercise increases lactate delivery into the brain and cerebral blood flow in humans[114] Intravenous lactate infusion decreases brain glucose uptake and enhances oxygen consumption in humans[114,115] Lactate protects cerebral function during hypoglycaemia: elevating lactate (within a normal range) substantially reduces symptomatic responses to hypoglycaemia in humans[116]
SFAs	Adipose tissue	Ingestion of SFA-enriched diets is associated with increased risk of BBB dysfunction and neurovascular inflammation in mice[117] Natural SFAs, like lauric acid, preserve brain microvascular function, reducing infarct volumes and brain oedema during ischaemic insults, even with acute hyperglycaemia in mice[118] Intra-arterially infused SFA emulsions open the BBB through tight junctions and promote drug delivery into the brain in rats[119] Intracerebroventricular SFA infusion enhances NF-κB-mediated inflammation at the BBB via TLR4 receptor in mice[120]

BBB, blood–brain barrier; BHB, β-hydroxybutyrate; NVU, neurovascular unit; SFAs, saturated fatty acids.

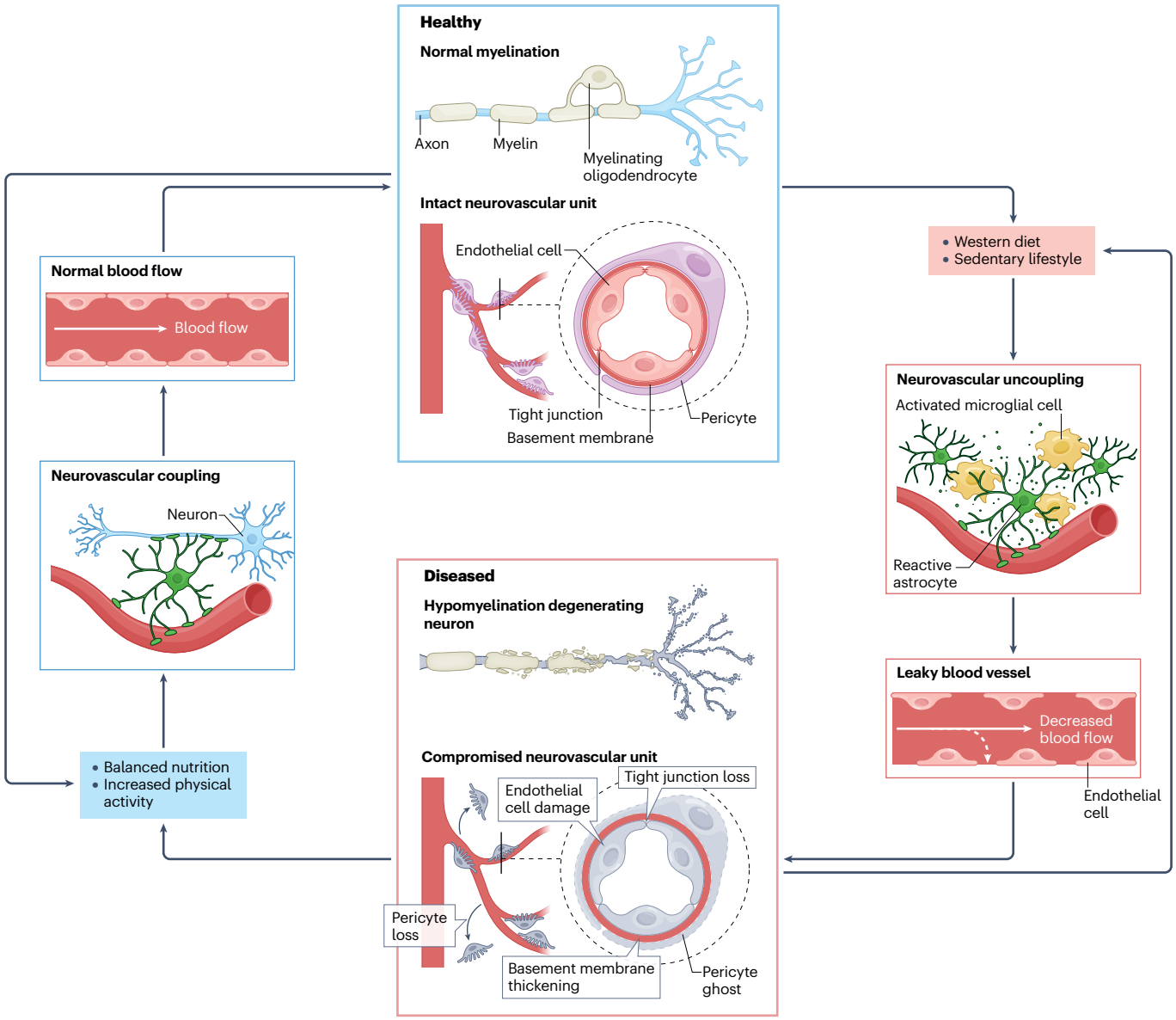

Fig. 2 | The effects of lifestyle on neurovascular health. A sedentary lifestyle paired with an obesogenic Western diet (ultra-processed food with high-fat and high-sugar content) leads to neurovascular uncoupling and microvascular dysfunction, resulting in neuroinflammation, cognitive decline and an increased risk of neurodegeneration. These changes lead 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.

observations, several pieces of evidence point to a positive effect of intermittent fasting on neurovascular functions. For instance, preconditioning mice with intermittent fasting (>16 h of fasting per day) for 4 months prior to disease pathology results in a substantial reduction in chronic cerebral hypoperfusion-induced neurovascular pathologies[57]. This reduction is achieved by attenuated microvascular leakage, which enhanced BBB integrity, prevented tight junction breakdown, reduced white matter injury and minimized neuronal loss[57]. Additionally, in a rat model of middle cerebral artery occlusion, 3 months of preconditioning with intermittent fasting (8-h feeding window per day) ameliorates the neurological severity score and adhesive removal test and increases microvessel density[58]. Moreover, in a mouse model of subcortical vascular dementia, postconditioning (intervention after disease induction) with intermittent fasting (6-h feeding window per day) for a month substantially attenuates cognitive impairments and neuronal loss without affecting the cerebrovasculature and white matter[59].

These findings suggest that further investigations into the effect of intermittent fasting on NVC in brain regions that control energy homeostasis could 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 effect of intermittent fasting on the NVU, and whether these effects translate into a positive

feedback loop on neurometabolic functions. To fully harness the potential of intermittent fasting as an interventional tool, it is imperative to explore its effects in a variety of settings, using different models of preconditioning and postconditioning across various age groups. This comprehensive approach is essential to uncover the full spectrum of benefits and limitations associated with intermittent fasting and neurological health.

Caloric restriction

Compared with intermittent fasting, the mechanistic link between food intake and neurovascular functions is better understood in models of caloric restriction. In rodents, most caloric restriction models range from 10% to 50% of caloric restriction from baseline, whereas in humans, most interventions aim for 10–25% caloric restriction per day[47]. Caloric restriction in rodents leads to reductions in neuroinflammation and oxidative stress[60]. In healthy adults without obesity, a 2-year regimen of 25% caloric restriction leads to substantial improvements in working memory[61,62]. Notably, the benefits of caloric restriction extend beyond these healthy populations to individuals with various medical conditions. For patients with multiple sclerosis, a 12-week caloric restriction diet (2 days per week with under 500 kcals) results in improved brain health[63], associated with elevated regional cerebral blood flow in the bilateral inferior temporal gyri and bilateral fusiform gyri[63]. The underlying mechanisms still require further clarification.

Preclinical studies suggest that the neuroprotective effects of caloric restriction involve neurovascular coupling. In young mice, 40% caloric restriction enhances cerebral blood flow and improves BBB function by inhibiting mTOR expression and enhancing endothelial nitric oxide synthase signalling[64]. These effects are also observed in aged mice, where caloric restriction helps maintain cerebral blood flow in the hippocampus and frontal cortex, thereby preserving learning and long-term memory, and reducing anxiety[64]. In aged rats, 6 months of 40% caloric restriction enhances vascular tone in cerebral and mesenteric arteries, with minor effects on vascular remodelling[65]. Moreover, in diet-induced overweight mice, 12 weeks of 30% caloric restriction improves BBB leakage and glial activation by reducing neurogranin-associated calcium signalling[66]. When long-term 40% caloric restriction was applied in an aged and obese rat model, it improved oxidative stress and inflammation and increased plasma levels of adiponectin[67]. As an insulin sensitizer, adiponectin has a fundamental role in vascular physiology by regulating glucose uptake[68]. Disrupted adiponectin signalling is reported in various neurovascular diseases; therefore, the capability of caloric restriction to ameliorate plasma adiponectin levels points to a possible mechanism through which caloric restriction enacts its neuroprotective effects[68].

Studies have investigated the potential of caloric restriction for neuroprotection in a range of neurological diseases. Even in mice at a very early age (postnatal day 7), moderate caloric restriction (achieved by having 18 pups per dam) offers protection against hypoxic ischaemia, with benefits attributed to the suppression of p53 expression in the NVU[69]. This suppression leads to reduction in neurovascular damage and a decrease in microglial activation[69]. A preconditioning approach with 4 weeks of 30% caloric restriction in mice protects against transient focal ischaemia-induced infarct by enhancing glucose metabolism and promoting adiponectin secretion[70]. In aged rats, an 8-week programme of 30% caloric restriction preceding experimental infarction prevents stroke-induced weight loss and enhances overall behavioural and metabolic recovery[71]. This protective effect is suggested to be partly mediated through gut microbiota[72]. In a mouse model of transient middle cerebral artery occlusion, postconditioning with 3 days of caloric restriction reduces infarct volume, while postconditioning with 56 days of 35% caloric restriction promotes recovery in post-ischaemia motor coordination[73]. This approach increases long-term neuronal survival and brain capillary density and reduces brain atrophy in the peri-infarct striatum[73]. To unravel the mechanisms that underlie caloric restriction-induced neuroplasticity, further studies are required to understand the intricate interplay between circulating metabolites and modifications to the NVU structure.

The impact of both intermittent fasting and caloric restriction on obesity depends on the reversibility of obesity-induced neurovascular decoupling, cerebrovascular rewiring and cognitive decline. This reversibility hinges on the severity of obesity. However, studying how the neurovascular system reacts to these interventions in the context of obesity could help reverse its long-term alterations. Practicing intermittent fasting or caloric restriction in adults with overweight or obesity enhances cognitive performance in tasks thought to involve hippocampal function, yet no differences are seen between the caloric restriction and intermittent fasting regimens[74,75]. Among patients with obesity and mild cognitive impairment, a 12-month caloric restriction regimen (nutritional counselling with a recommended calorie deficit of 500 kcal per day) leads to improvements in memory, executive function, global cognition and language[76]. This improvement was more pronounced in younger patients and carriers of the *APOE4* allele, a variant of *APOE* that causes vascular defects associated with Alzheimer disease[76]. In middle-aged adults (mean age of 45 years) with overweight or obesity, a 12-month intervention involving diet (1,200 to 1,800 kcal per day based on baseline body weight) and exercise leads to a 10% weight loss and increased cerebral blood flow in frontal, parietal and subcortical regions[77]. Intriguingly, the combination of diet and exercise seems to modulate cerebral blood flow in a region-specific manner[77].

Physical activity

Energy homeostasis is achieved through an intricate balance between energy intake and energy expenditure. Energy expenditure takes various forms, including basal metabolic rate, thermogenesis and physical activity[78,79]. Basal metabolic rate and thermogenesis are vital components of energy expenditure; however, in the context of neurovascular coupling, most evidence highlights the importance of physical activity[80]. Moreover, physical activity is tunable in a voluntary manner. Thus, physical activity 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 increase in people who live a sedentary lifestyle in Western societies has elevated all-cause mortality and the risks for metabolic and neurological diseases[81]. Several physical activity interventions have been proposed to reduce disabilities and lengthen healthspan[82]. Although the metabolic benefits of physical activity (for example, improved blood lipid profiles) and its effect on neurological health (for example, migraine prevention) have been thoroughly investigated[83,84], the molecular mechanisms underlying the benefits of physical activity on the cerebral vascular system need to be deciphered.

Chronic aerobic exercise is linked to improved cognition, a reduction in depression and anxiety[85,86], white matter plasticity, and performance of episodic memory[87]. Physical activity is a widely adopted intervention to supplement pharmacology in the treatment of neurodegenerative diseases[88–91]. The link between physical activity and

neuroplasticity could in part involve the upregulation of an array of neurotrophic factors, including brain-derived neurotrophic factor[92,93]. In sedentary adults with overweight or obesity, undertaking an aerobic programme for 8 weeks reinstates brain insulin sensitivity[94]. Compared with adults with a healthy weight, the response of cerebral blood flow to intranasal insulin differs for adults with overweight or obesity, with increased cerebral blood flow in the middle frontal gyrus but decreased flow in cortico-limbic regions[95]. The potential of lifestyle interventions to mitigate obesity-induced neuroinflammation and insulin resistance as well as restoring various signalling pathways requires further investigation into how nutrient shifts affect neurovascular coupling. The consensus in all the outlined studies is that physical activity for patients in general alters neurovascular coupling and cerebral blood flow, with structural changes in the cerebrovasculature potentially occurring in chronic interventions.

Supporting this notion, several preclinical studies have shown that neurovascular properties are affected by exercise. Studies in the rat motor cortex have unveiled the induction of angiogenesis, an increase in cerebral blood volume and heightened metabolism upon exercise[96]. In mice, physical activity can prevent cerebrovascular damage and white matter loss caused by 10 months of HFD feeding[97]. Although physical activity led to weight loss, active HFD mice remained notably heavier than sedentary control mice[97]. This finding suggests that the benefits of physical activity on brain health are partly independent of weight loss. Physical activity reduces the interaction between MBP (a marker involved in myelination) and IBA1 (a marker specific for microglia and macrophages), limits the number of $CD68^+$ cells (a marker of activated or phagocytic cells), and mitigates the reduction in endothelial cells and pericytes in the frontal partial cortex and corpus callosum, without notably preventing the myelin loss that is seen with HFD feeding[97]. The mechanisms involved in obesity-induced neurovascular decoupling and cerebrovascular rewiring require further investigation as does whether these cerebral shifts are reversible in response to lifestyle interventions.

Still, these findings underscore a direct link between exercise and enhanced neurovascular coupling. The connection between exercise and neuroprotection is partly explained by an enhancement of 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 CO_2 (ref. 85). Compared with sedentary individuals, active individuals have higher resting intracranial blood velocity and lower cerebrovascular reactivity in the middle and posterior cerebral arteries[98,99]. Both cerebral blood flow and cerebrovascular reactivity decrease with age but physical activity assists in preserving or enhancing these factors in healthy individuals[100]. A possible explanation for reduced cerebrovascular reactivity in active individuals is that chronic exposure to elevated CO_2 concentration due to frequent exercise results in desensitization of the cerebrovasculature to CO_2, thereby leading to a lack of vasodilation.

Together, lifestyle interventions are effective interventions to extend lifespan and healthspan and for the prevention and treatment of metabolic and neurological diseases[101]. By changing the whole-body metabolic profile, these interventions probably affect the cerebral landscape through direct and indirect mechanisms. While their effects on cerebrovascular health largely overlap, distinct nuances can be observed between the effects of intermittent fasting, caloric restriction and physical activity (Box 2). Therefore, further research is required to distinguish the physiological and molecular differences over time according to 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 complementary to pharmacological treatments for the metabolic and neurological diseases associated with overnutrition and a sedentary lifestyle. Although pharmacological interventions lead to a greater weight loss compared with 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 pharmaceutical usage and minimize weight rebound[45].

Box 2 | Major effects of lifestyle interventions on the neurovascular unit

Intermittent fasting

- Attenuates microvascular leakage and tight junction breakdown and enhances blood–brain barrier (BBB) integrity after cerebral hypoperfusion in mice[57].
- Increases microvessel density and ameliorates cognitive function after middle cerebral artery occlusion in rats[58].
- Attenuates neuronal loss after subcortical vascular dementia in mice[59].

Caloric restriction

- Enhances regional cerebral blood flow and BBB function in mice[64].
- Regulates vascular tone in cerebral and mesenteric arteries in rats[65].
- Mitigates obesity-induced BBB leakage and glial activation in mice[66].
- Reduces neurovascular damage and neuroinflammation after hypoxic ischaemia in mice[69].

Physical activity

- Enhances regional cerebral blood flow in the middle frontal gyrus and attenuates cerebral blood flow in cortico-limbic regions in humans[95].
- Induces angiogenesis and increases cerebral blood volume in rats[96].
- Mitigates loss of endothelial cells and pericytes by reducing neuroinflammation in obese mice[97,99].
- Elevates resting intracranial blood velocity and reduces cerebrovascular reactivity in humans[98].

Conclusions

Neurovascular coupling has a fundamental role in energy balance regulation, serving as an intermediary that facilitates the communication between central and peripheral systems. Understanding the effect of lifestyle interventions on cerebrovascular health strengthens their effectiveness in complementing pharmacological interventions for metabolic disease. The uncoupling of the neurovascular network that is observed in obesity indicates that a connection exists between overnutrition and cognitive decline as well as neurological diseases. Establishing strong mechanistic links between the alterations of the neurovascular system in key brain regions and metabolic disorders and

how these are positively affected by lifestyle interventions remains a promising avenue to complement the currently available pharmacological treatments of obesity. Whether the benefits exerted by lifestyle interventions on the neurovascular landscape are through a direct mechanism or occur indirectly by inducing overall weight loss remains to be elucidated. Nonetheless, it is evident that these interventions demonstrate beneficial effects on the neurovascular landscape and can be utilized as tools to combat the pathological rewiring of the NVU and cerebrovasculature. In conjunction with pharmacological therapies, lifestyle modifications provide an opportunity to prevent the development of obesity and its comorbidities.

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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 (2021).
2. Banks, W. A. The blood-brain barrier as an endocrine tissue. *Nat. Rev. Endocrinol.* **15**, 444–455 (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 (2018).
4. Ayloo, S. & Gu, C. Transcytosis at the blood-brain barrier. *Curr. Opin. Neurobiol.* **57**, 32–38 (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 (2019).
6. Iadecola, C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron* **96**, 17–42 (2017).
7. Vanlandewijck, M. et al. A molecular atlas of cell types and zonation in the brain vasculature. *Nature* **554**, 475–480 (2018).
8. Hillman, E. M. Coupling mechanism and significance of the BOLD signal: a status report. *Annu. Rev. Neurosci.* **37**, 161–181 (2014).
9. Kirst, C. et al. Mapping the fine-scale organization and plasticity of the brain vasculature. *Cell* **180**, 780–795.e25 (2020).
10. Gruber, T. et al. Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab.* **33**, 1155–1170.e10 (2021).
11. Jais, A. & Bruning, J. C. Arcuate nucleus-dependent regulation of metabolism-pathways to obesity and diabetes mellitus. *Endocr. Rev.* **43**, 314–328 (2022).
12. Prevot, V. et al. The versatile tanycyte: a hypothalamic integrator of reproduction and energy metabolism. *Endocr. Rev.* **39**, 333–368 (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 (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 (2020).
15. Jiang, H. et al. MCH neurons regulate permeability of the median eminence barrier. *Neuron* **107**, 306–319 e309 (2020).
16. Hosli, L. et al. Direct vascular contact is a hallmark of cerebral astrocytes. *Cell Rep.* **39**, 110599 (2022).
17. Marina, N. et al. Brain metabolic sensing and metabolic signaling at the level of an astrocyte. *Glia* **66**, 1185–1199 (2018).
18. Yi, C. X. et al. High calorie diet triggers hypothalamic angiopathy. *Mol. Metab.* **1**, 95–100 (2012).
19. McManus, R. et al. Dynamic response of cerebral blood flow to insulin-induced hypoglycemia. *Sci. Rep.* **10**, 21300 (2020).
20. Li, Z. et al. Bridging metabolic syndrome and cognitive dysfunction: role of astrocytes. *Front. Endocrinol.* **15**, 1393253 (2024).
21. Hernandez-Garzon, E. et al. The insulin-like growth factor I receptor regulates glucose transport by astrocytes. *Glia* **64**, 1962–1971 (2016).
22. Garcia-Caceres, C. et al. Astrocytic insulin signaling couples brain glucose uptake with nutrient availability. *Cell* **166**, 867–880 (2016).
23. Jais, A. et al. Myeloid-cell-derived VEGF maintains brain glucose uptake and limits cognitive impairment in obesity. *Cell* **165**, 882–895 (2016).
24. 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 (2023).
25. 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 (2020).
26. Glodzik, L. et al. Higher body mass index is associated with worse hippocampal vasoreactivity to carbon dioxide. *Front. Aging Neurosci.* **14**, 948470 (2022).
27. Knight, S. P. et al. Obesity is associated with reduced cerebral blood flow — modified by physical activity. *Neurobiol. Aging* **105**, 35–47 (2021).
28. Chhabria, K. et al. The effect of hyperglycemia on neurovascular coupling and cerebrovascular patterning in zebrafish. *J. Cereb. Blood Flow Metab.* **40**, 298–313 (2020).
29. 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 (2022).
30. 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 (2013).
31. Gomez-Smith, M. et al. Reduced cerebrovascular reactivity and increased resting cerebral perfusion in rats exposed to a cafeteria diet. *Neuroscience* **371**, 166–177 (2018).
32. Livingston, J. M. et al. Influence of metabolic syndrome on cerebral perfusion and cognition. *Neurobiol. Dis.* **137**, 104756 (2020).
33. 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**, 2840 (2019).
34. Nam, K. W. et al. Obesity without metabolic disorder and silent brain infarcts in aneurologically healthy population. *Int. J. Obes.* **44**, 362–367 (2020).
35. 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 (2021).
36. Rhea, E. M. et al. Blood-brain barriers in obesity. *AAPS J.* **19**, 921–930 (2017).
37. Collignon, A., Dion-Albert, L., Menard, C. & Coelho-Santos, V. Sex, hormones and cerebrovascular function: from development to disorder. *Fluids Barriers CNS* **21**, 2 (2024).
38. 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 (2017).
39. 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 (2023).
40. 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**, 2860 (2021).
41. Bianco, A., Antonacci, Y. & Liguori, M. Sex and gender differences in neurodegenerative diseases: challenges for therapeutic opportunities. *Int. J. Mol. Sci.* **24**, 6354 (2023).
42. Abi-Ghanem, C., Robison, L. S. & Zuloaga, K. L. Androgens' effects on cerebrovascular function in health and disease. *Biol. Sex Differ.* **11**, 35 (2020).
43. 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 (2019).
44. 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 (2021).
45. Wadden, T. A., Tronieri, J. S. & Butryn, M. L. Lifestyle modification approaches for the treatment of obesity in adults. *Am. Psychol.* **75**, 235–251 (2020).
46. Cavalcanti-de-Albuquerque, J. P. & Donato, J. Jr. Rolling out physical exercise and energy homeostasis: focus on hypothalamic circuitries. *Front. Neuroendocrinol.* **63**, 100944 (2021).
47. 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 (2022).
48. Tsurugizawa, T., Djemai, B. & Zalesky, A. The impact of fasting on resting state brain networks in mice. *Sci. Rep.* **9**, 2976 (2019).
49. Varady, K. A., Cienfuegos, S., Ezpeleta, M. & Gabel, K. Clinical application of intermittent fasting for weight loss: progress and future directions. *Nat. Rev. Endocrinol.* **18**, 309–321 (2022).
50. de Cabo, R. & Mattson, M. P. Effects of intermittent fasting on health, aging, and disease. *N. Engl. J. Med.* **381**, 2541–2551 (2019).
51. 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 (2017).
52. Currenti, W. et al. Association between time restricted feeding and cognitive status in older Italian adults. *Nutrients* **13**, 191 (2021).
53. 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.e3 (2018).
54. 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**, 2644 (2020).
55. Baik, S. H., Rajeev, V., Fann, D. Y., Jo, D. G. & Arumugam, T. V. Intermittent fasting increases adult hippocampal neurogenesis. *Brain Behav.* **10**, e01444 (2020).
56. 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 (2022).
57. 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 (2022).
58. 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 (2023).
59. 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 (2021).

60. 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 (2021).
61. Leclerc, E. et al. The effect of caloric restriction on working memory in healthy non-obese adults. *CNS Spectr.* **25**, 2–8 (2020).
62. 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 (2017).
63. Rahmani, F. et al. 12-weeks of caloric restriction diet improves cortical cerebral blood flow in healthy middle-age adults. *Alzheimers Dement.* **19**, e060865 (2023).
64. Parikh, I. et al. Caloric restriction preserves memory and reduces anxiety of aging mice with early enhancement of neurovascular functions. *Aging* **8**, 2814–2826 (2016).
65. Tropea, T. & Mandala, M. Caloric restriction enhances vascular tone of cerebral and mesenteric resistance arteries in aged rats. *Mech. Ageing Dev.* **197**, 111520 (2021).
66. 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 (2016).
67. 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**, 532 (2020).
68. Opatrilova, R. et al. Adipokines in neurovascular diseases. *Biomed. Pharmacother.* **98**, 424–432 (2018).
69. 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 (2012).
70. 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 (2019).
71. Ciobanu, O. et al. Caloric restriction stabilizes body weight and accelerates behavioral recovery in aged rats after focal ischemia. *Aging Cell* **16**, 1394–1403 (2017).
72. Huang, J. T. et al. Calorie restriction conferred improvement effect on long-term rehabilitation of ischemic stroke via gut microbiota. *Pharmacol. Res.* **170**, 105726 (2021).
73. 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 (2021).
74. 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**, 638 (2020).
75. 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 (2021).
76. 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 (2016).
77. Stillman, C. M. et al. Changes in cerebral perfusion following a 12-month exercise and diet intervention. *Psychophysiology* **58**, e13589 (2021).
78. Loffler, M. C. et al. Challenges in tackling energy expenditure as obesity therapy: from preclinical models to clinical application. *Mol. Metab.* **51**, 101237 (2021).
79. Soares, M. J. & Muller, M. J. Resting energy expenditure and body composition: critical aspects for clinical nutrition. *Eur. J. Clin. Nutr.* **72**, 1208–1214 (2018).
80. 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 (2023).
81. 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 (2020).
82. Qiu, Y. et al. Exercise sustains the hallmarks of health. *J. Sport Health Sci.* **12**, 8–35 (2023).
83. Thyfault, J. P. & Bergouignan, A. Exercise and metabolic health: beyond skeletal muscle. *Diabetologia* **63**, 1464–1474 (2020).
84. Di Liegro, C. M., Schiera, G., Proia, P. & Di Liegro, I. Physical activity and brain health. *Genes* **10**, 720 (2019).
85. Guadagni, V. et al. Aerobic exercise improves cognition and cerebrovascular regulation in older adults. *Neurology* **94**, e2245–e2257 (2020).
86. Harvey, S. B. et al. Exercise and the prevention of depression: results of the HUNT cohort study. *Am. J. Psychiatry* **175**, 28–36 (2018).
87. Mendez Colmenares, A. et al. White matter plasticity in healthy older adults: the effects of aerobic exercise. *NeuroImage* **239**, 118305 (2021).
88. Broadhouse, K. M. et al. Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. *NeuroImage Clin.* **25**, 102182 (2020).
89. 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 (2022).
90. 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 (2023).
91. 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 (2019).
92. Sleiman, S. F. et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. *eLife* **5**, e15092 (2016).
93. 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 (2020).
94. Kullmann, S. et al. Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. *JCI Insight* **7**, e161498 (2022).
95. 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 (2023).
96. 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 (2003).
97. Graham, L. C. et al. Exercise prevents obesity-induced cognitive decline and white matter damage in mice. *Neurobiol. Aging* **80**, 154–172 (2019).
98. Bailey, D. M. et al. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. *Stroke* **44**, 3235–3238 (2013).
99. Thomas, B. P. et al. Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO_2. *J. Magn. Reson. Imaging* **38**, 1177–1183 (2013).
100. 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* **35**, 905–920 (2013).
101. Espeland, M. A. et al. Long term effect of intensive lifestyle intervention on cerebral blood flow. *J. Am. Geriatr. Soc.* **66**, 120–126 (2018).
102. Avraham, Y. et al. Leptin induces neuroprotection neurogenesis and angiogenesis after stroke. *Curr. Neurovasc. Res.* **8**, 313–322 (2011).
103. Cui, Q. et al. Leptin promotes angiogenesis via pericyte STAT3 pathway upon intracerebral hemorrhage. *Cells* **11**, 2755 (2022).
104. Fernandez, A. M. et al. Insulin regulates neurovascular coupling through astrocytes. *Proc. Natl Acad. Sci. USA* **119**, e2204527119 (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 (2003).
106. Warmke, N. et al. Pericyte insulin receptors modulate retinal vascular remodeling and endothelial angiopoietin signaling. *Endocrinology* **162**, 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 (2020).
108. Chen, A. Q. et al. Microglia-derived TNF-α mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. *Cell Death Dis.* **10**, 487 (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 (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 (2018).
112. Hasselbalch, S. G. et al. Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am. J. Physiol.* **270**, E746–751 (1996).
113. Ma, D. et al. Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Sci. Rep.* **8**, 6670 (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 (2009).
115. Ide, K., Schmalbruch, I. K., Quistorff, B., Horn, A. & Secher, N. H. Lactate, glucose and O_2 uptake in human brain during recovery from maximal exercise. *J. Physiol.* **522**, 159–164 (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 (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 (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**, 3342 (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**, 246 (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 (2009).
121. Renaudin, N. et al. Functional ultrasound localization microscopy reveals brain-wide neurovascular activity on a microscopic scale. *Nat. Methods* **19**, 1004–1012 (2022).
122. 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 (2022).

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Author contributions

M.S. and B.C. researched data for the article. M.S., B.C. C.G.C., A.E. and N.R. contributed substantially to discussion of the content. M.S., B.C., C.G.C., A.E. and N.R. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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