nature metabolism

Review article

https://doi.org/10.1038/s42255-024-01079-8

Obesity-induced inflammation: connecting the periphery to the brain

Received: 3 November 2022

Accepted: 11 June 2024

Published online: 12 July 2024

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Obesity is often associated with a chronic, low-grade inflammatory state affecting the entire body. This sustained inflammatory state disrupts the coordinated communication between the periphery and the brain, which has a crucial role in maintaining homeostasis through humoural, nutrient-mediated, immune and nervous signalling pathways. The inflammatory changes induced by obesity specifically affect communication interfaces, including the blood–brain barrier, glymphatic system and meninges. Consequently, brain areas near the third ventricle, including the hypothalamus and other cognition-relevant regions, become susceptible to impairments, resulting in energy homeostasis dysregulation and an elevated risk of cognitive impairments such as Alzheimer's disease and dementia. This Review explores the intricate communication between the brain and the periphery, highlighting the effect of obesity-induced inflammation on brain function.

Obesity has become a global pandemic and a major public health concern in most developed, but also developing, countries. Its effect on individuals has become even more important in recent years, as it poses potential issues for those dealing with other new pathologies such as coronavirus disease 2019. Therefore, understanding the mechanisms by which obesity comes into place and its effect on the body, both at the peripheral and central levels, is crucial to finding effective ways to tackle this disease, particularly when excess fat accumulation begins to affect health.

Most cases of obesity are associated with a chronic, low-grade inflammation throughout the body. Interestingly, the severity of symptoms is seemingly determined by an individual's capacity to safely store fat, rather than by body mass index (BMI) alone. When such a sustained inflammatory state occurs, weight gain happens more readily while weight loss becomes more challenging, interfering with overall health and increasing the risk of developing obesity-related pathologies such as type 2 diabetes (T2D), cardiovascular disease and certain types of cancer, among others. Although the brain is considered a 'privileged immune organ,' certain conditions such as infection and sickness have been shown to affect the inflammatory status[1,2] of the central nervous system (CNS) and disrupt the function of certain brain areas[3,4]. Moreover, obesity is also an aggravating factor for neurological conditions such as Alzheimer's disease (AD) and dementia, which develop gradually over time. Furthermore, increasing evidence strongly suggests potential interrelated mechanisms between a sustained inflammatory response in the brain and an impaired brain function, the two observed in both obesity[5] and AD pathogenesis[6,7].

Here, we review the latest findings in the field, highlighting the long-term consequences of obesity and how peripheral endocrine organs and associated immune responses influence energy homeostasis and cognitive function in both animal models and humans.

Systemic inflammation in obesity

As with other biological processes that ensure homeostasis and proper body function, the maintenance of a healthy weight and energy balance engage multi-organ systems, which are coordinated through complex multidirectional interactions and have their own regulatory mechanisms. Thus, the brain is able to communicate with its environment not only via circulating molecules—from the blood, cerebrospinal fluid (CSF), and so on—but also via innervation of the different organs, which allows fine-tuning of the processes guaranteeing homeostasis.

Specifically, maintaining energy homeostasis relies on a coordinated communication between endocrine organs such as the adipose tissue, gastrointestinal (GI) tract and brain, based on the information

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https://doi.org/10.1038/s42255-024-01079-8

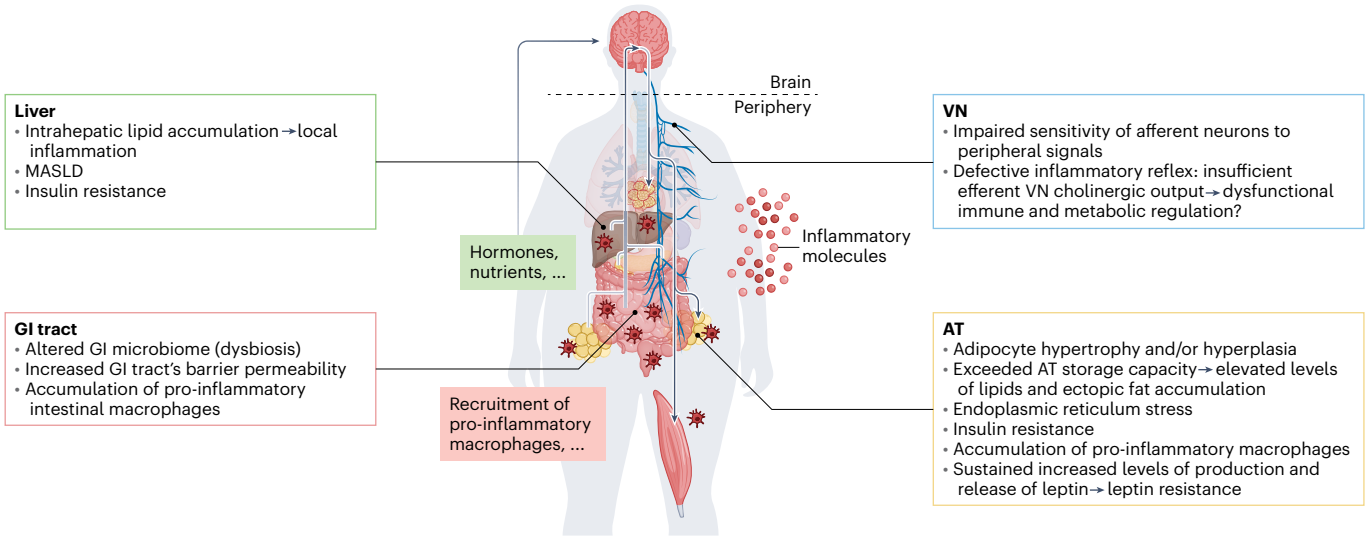

Fig. 1 | Periphery–brain interactions and immune responses in obesity. Energy homeostasis is maintained through a coordinated communication between endocrine organs and the brain, which involves the humoural pathway, the immune system and the parasympathetic nervous system (VN). With obesity, these systems can be disrupted, in association with increased inflammatory signalling and impaired communication with central circuits, potentially leading to the loss of proper regulation of whole-body energy homeostasis, but also cognitive defects. AT, adipose tissue.

they individually integrate. The immune system is also involved, with immune cells being part of the local environment, participating in the function of a given tissue, and potentially affecting the whole body. In the case of a prolonged exposure to a hypercaloric diet, the normal functioning of these peripheral systems can be disrupted, leading to inflammation and impaired communication with higher central circuits. Indeed, in pathological conditions associated with adipose tissue dysfunction, such as obesity, substantial alterations have been observed in the sensing, trafficking, uptake and/or utilization of signals emerging from the periphery into the brain[8] (Fig. 1). Notably, these changes also involve inflammatory immune responses, including increased levels of pro-inflammatory molecules, especially when the storage of body fat becomes pathological[9] (see Table 1 and Box 1 for the innovative methods to investigate periphery–brain interactions).

Adipose tissue

Adipose tissue, particularly white adipose tissue (WAT), is widely spread throughout the body, and serves as the largest energy reservoir in mammals. It is an integral part of the systems that maintain energy homeostasis and is specialized in storing energy in the form of lipids within its adipocytes when intake outmatches demand, providing stocks to be released when energy needs increase, for example, in times of fasting. The storage of energy causes the adipose tissue to expand via hypertrophy and/or hyperplasia of its adipocytes. Prolonged excessive energy intake can cause the adipose tissue to reach a limit in its storage capacity, which varies among individuals and leads to elevated circulating levels of lipids and ectopic fat accumulation. Moreover, adipocyte hypertrophy can trigger endoplasmic reticulum stress (a response that initiates a pro-inflammatory and/or apoptotic programme), leading to insulin resistance (IR). Adipocytes with IR become more lipolytic, causing an increase in free fatty acids that can activate the Toll-like receptor 4 (TLR4) and the nuclear factor kappa B (NF-κB) regulated pathways. This activation leads to the production and release of pro-inflammatory cytokines such as interleukin (IL)-6 or tumour necrosis factor (TNF), further promoting inflammation and WAT dysfunction.

Although adipose tissue is specialized in lipid storage, fat depots contain other cell types that coexist and interact locally, including stromal cells, endothelial cells and immune cells (macrophages, subsets of T cells and B cells). Several studies have also demonstrated that the accumulation of predominantly pro-inflammatory macrophages in the adipose tissue actually contributes to IR and glucose intolerance in obese mice and humans with obesity[10].

One other important aspect of WAT as an immune–endocrine organ is the production of bioactive molecules known as adipokines, which have a crucial role not only in metabolism, but also in controlling immunity and inflammation, thereby linking metabolic and immune responses. Among the different adipokines secreted by adipose tissue, leptin has garnered considerable attention for having a key role in metabolic disorders such as obesity since the cloning of the *ob* gene[11] and its purification[12] in 1994 and 1995, respectively. Through leptin, the adipose tissue communicates with the brain to regulate appetite and energy balance, ensuring an adequate energy supply to support physiological processes and body functions. Circulating levels of leptin generally mirror the amount of fat mass and satiety, and its expression can also increase during acute infection or inflammation. This dual function of leptin highlights the intricate connection between metabolic regulation and immune system modulation within WAT, particularly in response to changes in nutrient availability. Moreover, prolonged excessive energy intake can lead to adipose tissue dysfunction, characterized by sustained elevated circulating leptin levels that no longer accurately indicate the overall energy availability in the body. Gradual acquisition of leptin resistance, which refers to the state where leptin loses its anorectic effect in the brain, is widely recognized as a hallmark of weight gain in diet-induced obesity (DIO)[13].

Excessive energy intake also affects other endocrine organs such as the liver, pancreas, skeletal muscle and heart, among others. Elevated circulating levels of fatty acids can contribute to the development of IR in several organs[14]. For example, in humans, there is a direct correlation between triglyceride content in the muscle and the occurrence of IR. Furthermore, as previously mentioned, elevated circulating levels of lipids and other inflammatory mediators can promote ectopic fat storage and inflammation in other tissues. This can result in increased cytokine production and activation and infiltration of immune cells into the affected tissue, ultimately impairing their function.

The liver

The liver has a vital role in metabolism, nutrient storage, detoxification and immunity, maintaining energy balance by responding to nutrient and humoural signals. It regulates glucose and lipid metabolism,

https://doi.org/10.1038/s42255-024-01079-8

Table 1 | Circulating factors involved in the systemic inflammation and maladaptive periphery–brain interactions associated with obesity

Name	Main sources in periphery	Circulating levels	Periphery	CNS
TNF	Adipose tissue Liver Skeletal muscle Macrophages Type 1 helper T cells	↑	• Adipose tissue: impaired glucose metabolism regulation, IR, dampened uptake and storage capacity of fatty acids and glucose, changes in production of cytokines, adipokines (for example, leptin)[91] • Liver and skeletal muscle: ↑ lipids, ↓ insulin sensitivity and glycogenolysis[91] • Liver: promotes inflammation, IR and steatosis[91] • Pancreas: ↓ insulin secretion (in response to leptin), ↑ glucagon and amylin secretion[91,92] • Immune system: promotes inflammation; ↑ pro-inflammatory (for example, IL-6) and ↓ anti-inflammatory cytokine production, and T cell and macrophage activation[91]	• BBB: ↑ permeability[93] • Glial cells: activation of microglia and astrocytes, and promotion of local inflammation (for example, NF-κB)[94,95] • Neuronal circuits: ↑ anorexigenic POMC neurons activity, dose-dependent modulation of insulin and leptin signalling in the hypothalamus, neuronal damage, ↑ neuronal death (glutamate-mediated cytotoxicity + oxidative stress), synaptic plasticity impairments (→neurodegenerative diseases such as AD or PD), and disruption of neurotransmitters systems (for example, glutamate, GABA, dopamine) → mood disorders, cognitive issues and motor dysfunction[57,96]
IL-1β	Adipose tissue Macrophages Immune cells	↑	• Adipose tissue: IR, impaired glucose metabolism and transport in adipocytes[97] • Liver: ↑ lipids, promotes steatosis[98] • Skeletal muscle: promotes IR[99] • Pancreas: higher IL-1β levels leading to beta cell dysfunction/apoptosis and defects in insulin production[100] • Immune system: induces pro-inflammatory cytokine production (for example, IL-6), and immune cell activation and infiltration (for example, T cell, macrophage)[100]	• BBB: ↑ permeability[93,101] • Glial cells: activation of microglia and astrocytes, promotion of local inflammation, impairment of the protective effect of astrocytes on BBB integrity (downregulated sonic hedgehog signalling), (d) induction of production of pro-inflammatory cytokines by astrocytes[94,101] • Neuronal circuits: potential changes in synaptic plasticity, neuronal damage, ↑ neuronal death (glutamate-mediated cytotoxicity + oxidative stress), synaptic plasticity impairments (→neurodegenerative diseases such as AD or PD), and disruption of neurotransmitters systems (for example, glutamate, GABA, dopamine) → mood disorders, cognitive issues and motor dysfunction[102,103]
IL-6	Adipose tissue Liver Skeletal muscle Immune cells	↑	• Chronic increase of IL-6 levels associated with obesity can lead to an IL-6 resistance and its beneficial effects on glucose homeostasis, insulin secretion (GLP-1 secretion from L-cells and α-cells) and response to insulin (muscle)[104] • Adipose tissue: stimulates lipolysis, ↑ release of free fatty acids and promotes IR[104] • Liver: promotes IR and liver disease[104,105] • Skeletal muscle: promotes IR[104] • Pancreas: reduced insulin secretion[104] • Immune system: ambiguous effects with potential promotion of both pro-inflammatory and anti-inflammatory signalling pathways[106]	• BBB: ↑ permeability[93] • Glial cells: activation of microglia and astrocytes and promotion of local inflammation[94] • Neuronal circuits: dose-dependent dysregulation of energy balance, enhanced central IL-6 *trans*-signalling (soluble IL-6 receptor in the CSF) improves energy and glucose homeostasis by action on neurons of the paraventricular nucleus of the hypothalamus, dose-dependent and time-dependent effect on memory formation and neuronal survival, dysregulation of neurotransmitters such as serotonin → depression and anxiety[107–110]
TGFβ	Adipose tissue Macrophages Immune cells Liver	↑	• Adipose tissue: promotes adipocyte hypertrophy, inhibits adipocyte differentiation, promotes local inflammation, fibrosis and IR[111] • Liver: promotes hepatic fibrosis and hepatic dysfunction[111] • Skeletal muscle: defects in glucose uptake and IR[111] • Pancreas: precipitates IR and beta cell secretory dysfunction[111] • GI tract: ↑ gut permeability[111] • Immune system: promotes chronic low-grade inflammation[111]	• Glial cells: acts as anti-inflammatory factor by inhibiting microglia[112]
CCL2 (MCP-1)	Adipose tissue Macrophages	↑	• Adipose tissue: promotes macrophage infiltration → IR[113] • Liver: attracts macrophages to the liver, promotes local inflammation and steatosis[114] • GI tract: recruitment of pro-inflammatory macrophages → ↑ gut permeability + inflammasome activation → IR[115] • Immune system: promotes local inflammation in the different tissues populated by recruiting more immune cells[116]	• BBB: ↑ permeability[117] • Glial cells: activation of microglia and astrocytes and promotion of local inflammation[94] • Neuronal circuits: high CCL2 levels in the brain are associated with AD[118] • Mediates the recruitment of immune cells to the brain[119]

CCL2, CC-motif chemokine ligand 2 (also known as MCP-1, monocyte chemoattractant protein 1); GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; PD, Parkinson's disease.

disruptions of which can lead to metabolic disorders such as IR and fatty liver disease. The liver, an endocrine organ, releases hepatokines such as angiopoietins, bile acids and fibroblast growth factor 21 (FGF21) to communicate with distant tissues, including the brain. Dysfunction in the liver's inter-organ signalling pathways can disrupt energy balance regulation, contributing to metabolic disorders. Interestingly, liver failure is often associated with the activation of inflammatory pathways in the brain, characterized by microglial activation and the accumulation of pro-inflammatory cytokines. This liver-to-brain pro-inflammatory signalling involves both humoural and neural routes and mechanisms such as microglial activation followed by recruitment of monocytes, and alterations in the permeability of the blood–brain barrier (BBB)[15],

https://doi.org/10.1038/s42255-024-01079-8

BOX 1

Innovative techniques for periphery–brain interface exploration

In recent times, technology has been at the forefront of developing techniques that preserve the integrity of peripheral–brain interactions within organisms, enabling a deeper understanding of the diseases at the full-body scale.

For example, over the past few years, several laboratories have been dedicated to refining methods for tissue clearing. For instance, recent protocols such as 3DISCO[153], vDISCO[154,155] or wildDISCO[156] allow immunolabelling and clearing of human fetuses or whole organisms, which can then be three-dimensionally imaged using multiple fluorescence microscopy systems. This approach allows for detailed examination of cellular and molecular landscapes in human embryos, shedding light on the development and interaction of various physiological systems[153]. Moreover, it reveals previously overlooked or misunderstood anatomical structures, such as membranes, which would initially be merely considered to maintain the integrity of the entire organ. Importantly, these techniques are readily advancing our fundamental understanding of overarching phenomena that affect the entire organism, including cancer metastasis, immune infiltration, vascularization and innervation across organs. These advancements open new avenues for research in immunotherapy and the optimization of chemotherapy delivery[157].

For functional in vivo studies, other emerging techniques facilitate crossing a frontier in comprehending the brain's role in complex behaviour by monitoring and manipulating calcium activity in specific brain cell types while animals remain capable of moving and behaving freely in their environment. Preserving peripheral–brain connection, these techniques are pivotal in studies aimed at evaluating specific events to a particular task performance, such as recording neuronal activity changes in response to ingestion in freely moving mice. Although two-photon microscopy offers several advantages over one-photon microscopy, including enhanced tissue penetration, reduced phototoxicity and improved signal-to-noise ratio, the fixation of the animal can substantially affect the study outcomes and available options.

Optogenetics and fibre photometry have indeed revolutionized the field of neuroscience by enabling the activation or monitoring of a large number of cells, being a helpful tool for the study of bulk activity of specific cell populations and/or entire circuits. Apart from calcium sensors, other luminescent biosensors for neurotransmitters (for example, glutamate and GABA), neuromodulators (for example, dopamine and serotonin) and metabolites (for example, lactate) have also been engineered. This warrants a broader area of investigation, allowing for the exploration of cross-talk between neurons and non-neuronal cells, such as astrocytes. For example, a team recently described a flexible and versatile system supporting multicolour fibre photometry, as well as optogenetic manipulation by utilizing a fused fibre coupler[158]. More recently, a new generation of multifunctional, microelectronic probes and devices have been established for investigating gut–brain connections during behaviour[159]. With this new technology, one can adjust the properties of the fibres to the organs' specific requirements (for example, stiffer fibres that can reach deep cerebral structures versus softer fibres that do not disrupt the digestive organs such as the intestine). These polymer flexible fibres can contain electrodes, temperature sensors, micro light-emitting devices and microfluidic channels to deliver drugs that can be inserted into different organs of interest. The fibres can then be wirelessly controlled by an external modular control circuit allowing programmable light delivery (optogenetics) and recording. In this study, the authors have successfully influenced animal behaviour by manipulating the gut–brain axis[159].

However, fibre photometry still has limitations when it comes to microscale resolution. Fortunately, the recent introduction of miniscope technology enables us to visualize changes in activity at single-cell resolution, to study individual cell behaviour and how it may be influenced by anatomical location, even in deeper brain areas using gradient-index lenses, and function of proximity to specific cell types or structures (for example, vasculature and ventricles). Miniscopes, mounted on the head of a freely moving animal, require a more challenging implantation surgery, potentially having a greater effect on behaviour, but offer better resolution and more spatial information, which, as with fibre photometry, can also be combined with optogenetics.

Therefore, the implementation of these new techniques marks an inspiring turning point in neuroscience, and in biology in general, allowing the investigation of brain function at the single-cell resolution scale, intraregional functional heterogeneity of intricate circuits with particular vascular properties—such as those found in the hypothalamus—and interrogating periphery–brain communication simultaneously (more details in 'Hypothalamic dysfunction in obesity').

a hallmark of many CNS diseases, all of which may contribute to the initiation of an immune response in the brain.

The relevance of liver–brain signalling in metabolic control is particularly evident with the action of FGF21 in the brain. This primarily liver-derived hormone binds to cell-surface receptors with β-klotho as a co-receptor, found in peripheral organs such as brown adipose tissue (BAT), WAT and specific brain areas including the hypothalamus and hindbrain. During fasting or with a ketogenic diet, FGF21 levels rise to promote fatty acid oxidation, ketogenesis and gluconeogenesis while simultaneously suppressing insulin secretion and promoting insulin sensitivity in peripheral tissues. Likewise, it increases energy expenditure and reduces body weight and hepatic triglycerides. This adaptive multi-organ response helps to maintain energy balance and glucose homeostasis during periods of nutrient deprivation. The role and effects of FGF21 appear to be largely dependent on the source tissue and general status. For example, brain-derived FGF21 regulates spatial memory formation, but not metabolism, unlike FGF21 derived from the liver[16]. In the context of obesity, circulating FGF21 levels have been found elevated, together with a blunted effect with exogenous FGF21, suggestive of a resistance state[17] that may result from impaired receptor signalling or downstream signalling pathways in target tissues, further contributing to metabolic dysfunction. However, it has been demonstrated that pharmacological doses of FGF21 can lead to reduced body weight and circulating glucose and insulin concentrations via sympathetic outflow to BAT and WAT in diet-induced obese mice, in a neuronal β-klotho-dependent manner (hypothalamus and dorsal vagal complex)[18]. Furthermore, a recent study in rodents has shown that delayed weaning (prolonged suckling) leads to long-lasting beneficial metabolic effects and protection against DIO in the progeny. This effect is mediated by an increase in hepatic FGF21 production in the offspring, which enters the brain via tanycytes and acts on neurons of the lateral hypothalamic area and zona incerta, leading to increased BAT activity, associated with higher energy expenditure, lower body weight and fat mass, and overall metabolic improvements[19].

This highlights the importance of the nervous system in mediating the beneficial weight loss and glycaemic effects of FGF21.

Furthermore, in obesity, higher levels of circulating fatty acids lead to intrahepatic lipid accumulation, which promotes local inflammation and the development of metabolic dysfunction-associated steatotic liver disease (MASLD) and potentially steatosis[20]. The presence of steatosis or a high number of intrahepatic triglycerides (IHTGs) is often associated with various metabolic abnormalities characterized by decreased insulin sensitivity in the liver, muscle and adipose tissue, as well as alterations in fatty acid and lipoprotein metabolism. MASLD encompasses a range of conditions featured by liver steatosis and IR and is closely related to inflammation, fibrosis, limited expandability and dysfunction, which contribute to the development of metabolic and cardiovascular disorders such as obesity, hypertension and T2D[21,22]. Interestingly, human studies have shown that MASLD correlates with a reduction in total cerebral brain volume, independent of visceral adipose tissue and cardiometabolic risk factors, suggesting a possible connection between hepatic steatosis and brain ageing[23].

Calorie restriction and weight loss have shown to be effective therapeutic approaches for individuals with both obesity and MASLD, resulting in a notable reduction in IHTG content and improved insulin sensitivity in the liver and muscle. However, it remains unclear whether MASLD is a cause or consequence of metabolic dysfunction, including brain deterioration, or whether metabolic dysfunction itself contributes to IHTG accumulation, or even whether both phenomena are perhaps interrelated. Not all individuals with obesity exhibit metabolic abnormalities in terms of IHTG content and some people appear to be protected from developing obesity-related diabetic complications[24].

The GI tract

The GI tract, the largest endocrine organ in the body, has a crucial role in metabolic regulation. It is composed of scattered enteroendocrine cells (EECs) distributed throughout the entire GI mucosa. Equipped with chemosensory machinery, EECs can detect nutritional and chemical signals and initiate appropriate functional responses to ensure dynamic control of energy homeostasis and/or circumvent noxious events. The GI tract provides constant input to the brain through various pathways, predominantly via EEC-produced gut hormones, such as incretins, that can enter the circulation to act on remote targets, or via vagal and spinal afferent neurons, immune mediators and microbiota-related signalling molecules[25]. Conversely, information from the brain to the gut is transmitted by autonomic neurons and neuroendocrine factors. Perturbations in the gut–brain axis have been observed in association with pathophysiological states linked to obesity. Indeed, defects in the gut–brain cross-talk, such as reduced neural activation in response to gut hormones that suppress appetite, have been proposed to further aggravate metabolic derailment in obesity[26,27]. Moreover, long-lasting exposure to hypercaloric diets and resulting obesity can also alter the composition of the GI microbiome, leading to marked changes in relation to microbiota species (dysbiosis) present, in both human and animal models. In healthy conditions, the intestinal epithelium acts as a barrier with its mucosal layer, preventing the transfer of substances and molecules from the GI tract into circulation. However, in obese conditions this barrier becomes more permeable, allowing some microbial or bacterial products such as lipopolysaccharides to enter the circulation[28]. These bacterial products can activate inflammasomes and in turn trigger inflammation. In addition, the integrity of the GI tract's barrier function can be influenced by certain nutrients, such as fructose. When metabolized in the GI tract, fructose has the potential to become toxic and weaken the protective barrier of the GI tract. This impairment can ultimately lead to dyslipidaemia and non-alcoholic steatohepatitis[29]. Moreover, gut inflammation, with accumulation of pro-inflammatory intestinal macrophages, is a hallmark of obesity in humans. Consequently, this translates into tissue dysfunction with higher circulating levels of pro-inflammatory cytokines and an increased number of activated immune cells in the periphery, which can potentially migrate to the brain and cause detrimental effects. Interestingly, studies in mice fed a hypercaloric diet have shown that depletion of intestinal-specific macrophages resulted in improved fasting glucose levels, glucose tolerance and insulin levels, suggesting a role of intestinal resident macrophages in glycaemic control[30].

The autonomic nervous system

The vagus nerve (VN) is the longest cranial, and the primary parasympathetic, nerve and is, therefore, a major communication pathway between the brain and the periphery. The VN innervates organs through efferent fibres originating from the brainstem[31]. Conversely, via afferent fibres, it conveys signals to the brainstem, particularly the nucleus tractus solitarius, which integrates sensory, hormonal and metabolic information to regulate physiological functions in higher brain regions. Through afferent projections to the GI tract and the hepatic portal system, the VN relays information about fluctuations in systemic metabolism to the brain[31]. Perturbations in the sensitivity of these VN afferent neurons to peripheral signals have been associated with weight gain in obesity. On the other hand, the VN regulates the cardiometabolic output via efferent innervations to the heart, liver or pancreas.

Additionally, the VN is capable of sensing peripheral inflammatory molecules through the expression of cytokine receptors (for example, IL-1β, TNF and TLR4, among others). It conveys these signals to the brain, triggering the release of acetylcholine into peripheral organs to regulate immune function and inhibits excessive pro-inflammatory cytokine production, and thus controls the progression of inflammation in the periphery—a physiological mechanism known as 'the inflammatory reflex'[31,32]. Insufficient efferent VN cholinergic output can contribute to dysfunctional immune and metabolic regulation observed in obesity[33]. Therefore, using electrical VN stimulation and cholinergic drugs to activate the cholinergic signalling of the efferent arm of the inflammatory reflex, which leads to metabolic and anti-inflammatory responses, represents a therapeutic strategy for limiting or alleviating the long-term consequences of inflammation associated with obesity and T2D[34].

The brain 'frontiers': both barriers and bridges

Proper brain function demands a homeostatic environment, that is, an adequate supply of molecules such as water, oxygen or nutrients from the periphery, but also clearance of waste products. The brain's functional requirements are met through dynamic adjustments in the cerebral blood flow, vascular function, immune responses and waste clearance. The supply of essential molecules and the elimination of waste require the communication between the brain and the periphery through physical barriers. Overall, a variety of systems are, therefore, involved in maintaining the health and functionality of the brain. These systems are nevertheless not infallible, as observed in cases of inflammation and obesity, especially with increased levels of pro-inflammatory markers, whether emanating from the periphery or being produced locally (Fig. 2 and Table 1).

The BBB: a flawed gateway in obesity

The neurovascular unit is an assemblage of functional brain cells formed by vascular cells, glial cells and neurons. It serves as both a physical barrier and an interactive system, with these cells responding to and secreting molecules that actively contribute to the regulation of processes necessary for proper brain function including cerebral blood flow, and both endocrine and immune responses[35].

The BBB is part of the neurovascular unit, composed of endothelial cells that form tight and adherens junctions, together with neurons and non-neuronal cells, which serve as an interface, both facilitating and controlling interactions between the periphery and the brain (Fig. 2). The BBB itself, through its interactions with pericytes and astrocytes, acquires a barrier phenotype that protects the brain under

https://doi.org/10.1038/s42255-024-01079-8

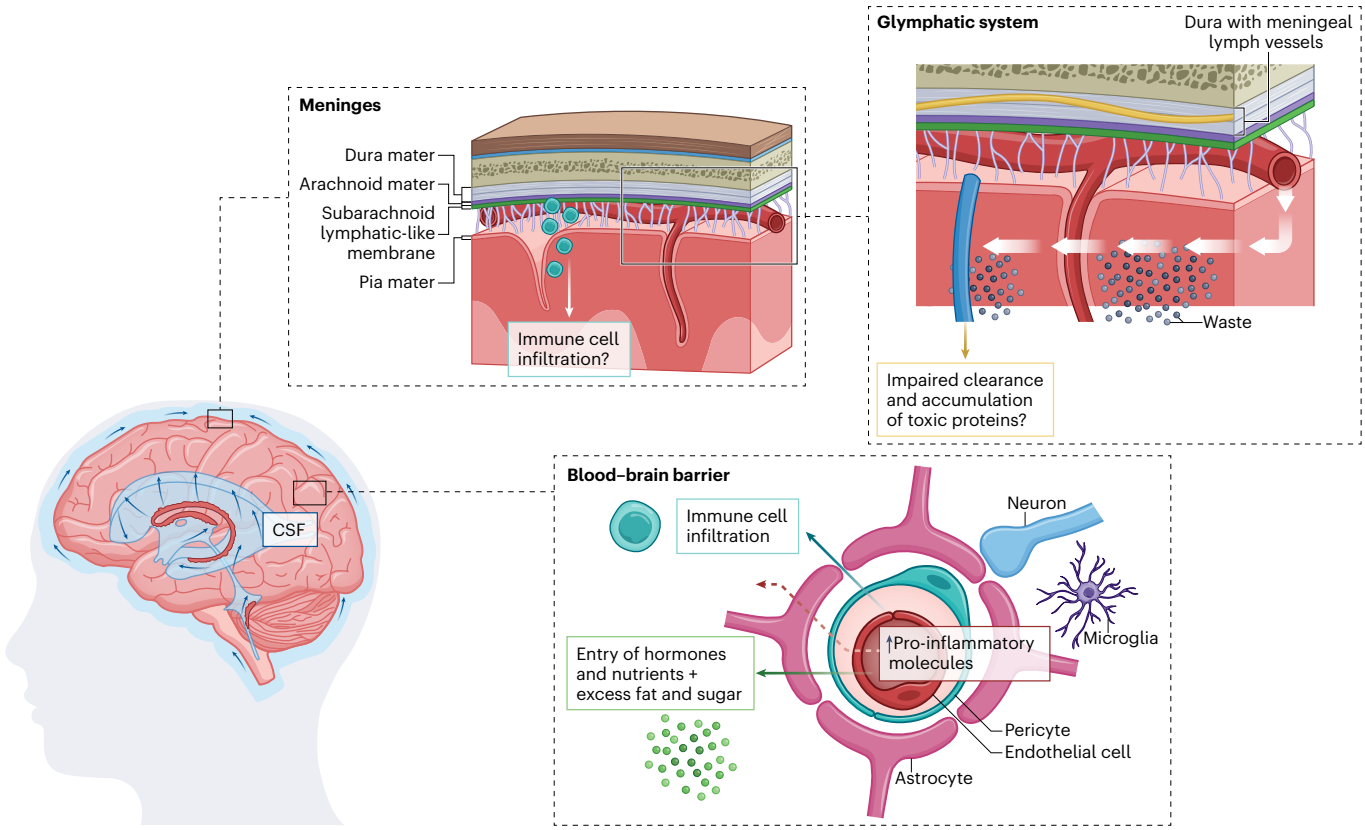

Fig. 2 | Brain 'frontiers'. Proper brain function requires a homeostatic environment, characterized by an appropriate supply of water, oxygen and nutrients from the periphery, in association with waste product clearance. This is ensured via the communication between the brain and the periphery through physical barriers such as the meninges, the BBB and the GS. Nevertheless, these systems can be impaired, as observed in association with inflammation and obesity.

physiological conditions. Generally, it limits the entrance of large blood-borne molecules and cells into the parenchyma and regulates the transport of other circulating elements such as nutrients and hormones[9].

This allows for maintaining an appropriate composition of the cerebral interstitial fluid (ISF) to guarantee proper neuronal activation. Additionally, in physiological conditions, cytokines present in the circulation can enter the brain through the intact BBB via a saturable transport system. Furthermore, the BBB does not negate the influence of hormones in the CNS, and in fact serves as an important conduit and interface for humoural-based communication between the brain and body in physiological conditions[36]. Of note, impairment of both cytokine and humoural transport across the BBB has been observed in obesity. Prolonged exposure to a hypercaloric diet leads to a substantial, chronic increase in the circulating levels of cytokines, which compromises the permeability of the BBB, as seen in other brain pathologies[37]. This allows both the entry of potentially harmful molecules and the recruitment of pro-inflammatory macrophages and leukocytes from the circulation into the cerebral parenchyma and CSF[3]. This could in turn affect the systems guaranteeing homeostasis in the brain. Interestingly, it has been shown that feeding a hypercaloric diet initially leads to a transient decrease in brain glucose uptake by reducing the expression of glucose transporter 1 on vascular endothelial cells of the BBB. However, with prolonged hypercaloric feeding, glucose transporter 1 expression is restored in endothelial cells, alongside increased recruitment of perivascular macrophages that express vascular endothelial growth factor (VEGF)-A. The myeloid cell-derived VEGF-A response observed in obesity has a crucial role in maintaining brain glucose uptake and mitigating cognitive impairment associated with obesity[38].

Meningeal lymphatic vessels and the GS

The brain lacks conventional lymphatic vessels to clear out its waste soluble products and metabolites from the ISF and CSF. Instead, it possesses an analogous waste clearance system named the 'glymphatic system' (GS), connected to a downstream lymphatic system, at the level of the meninges (dura), involving cranial nerves and larger meningeal vessels exiting the skull. Expectedly, this clearance system helps to maintain brain homeostasis, but it also has a crucial role in maintaining the population of native immune cells within perivascular spaces and meningeal membranes, while preventing the entry of undesired cells and pathogens into the CNS. Despite important progress in this emerging field, there is still much to uncover regarding the precise roles and interplay of meningeal lymphatics and the GS. It is of utmost importance to explore these aspects not only in the context of obesity, but also in relation to CNS repair processes and mechanisms responsible for the elimination of toxic proteins (for example, β-amyloid) from the brain. Failure of proper clearance could be linked to the development of neurodegenerative diseases such as AD and other neurological disorders associated with ageing and cognitive decline[39] (Box 2).

Meninges and meningeal lymphatic vessels. The meninges encase the brain and the spinal cord, cushioning them from the surrounding bone structures, and providing a controlled environment while bathing in CSF. Meninges have a crucial role in the brain's defence system, safeguarding its integrity. Recent research has challenged previous notions regarding the composition of the meninges, which were traditionally believed to comprise three layers: the dura mater, the arachnoid mater and the pia mater. The dura mater is the outermost and the thickest layer, offering robust protection and structural support. It facilitates the exit of blood from the brain and enables the re-entry of CSF into

https://doi.org/10.1038/s42255-024-01079-8

BOX 2

Recent human studies linking obesity and cognitive decline

Obesity has been associated with decreased cognitive function, both at the levels of memory performance and ability to learn[160]. In humans, study participants with obesity display a reduced activity in brain regions implicated in memory and learning processes when compared to lean individuals[161]. Human studies have consistently highlighted a strong association between inability to maintain a healthy weight or remain lean when reaching midlife and the propensity to developing, potentially early, neurodegenerative disorders such as AD and dementia[162,163]. Further research suggests that BMI trajectories across the lifespan can predict early development of dementia[164]. These findings underscore the critical importance of implementing early interventions leading to weight loss to reduce the incidence and delay the onset of dementia. Studies have shown that such measures have long-lasting cognitive protective effects, reduce the incidence of neurodegeneration and dementia and have even been associated with mitigating obesity-related brain neuropathy and cognitive impairment[165].

Moreover, a large prospective population-based approach has also revealed that midlife adiposity predicts the earlier onset of AD-related dementia, greater severity of neuropathology and increased brain amyloid deposition during ageing[162]. A recent study has also reported comparable cortical atrophy in people with obesity and those with AD, suggesting that some pathways could be shared in the pathogenesis of these two diseases[166].

Hormone resistance and inflammation have been highlighted as key risk factors participating in the neurodegeneration, which can lead to the thinning of cognitive-associated brain areas observed in both obesity and AD[167–169]. Normally, leptin and insulin have a protective function in the brain, helping to mitigate β-amyloid toxicity and facilitating its clearance[168,170]. However, in the context of obesity, excessive levels of fatty acids and these hormones in the circulation contribute to the accumulation of pathological protein aggregates and hinder their proper clearance in the brain[171]. Notably, elevated fasting plasma insulin levels have been linked to cognitive deficits and an increased risk of developing AD. Thus, the dysregulation of leptin and insulin in obesity can have detrimental effects on brain health and may contribute to the pathogenesis of AD. Furthermore, studies suggest that obesity-related BBB impairments involve glial activation, which can lead to synaptic defects, apoptosis, neurodegeneration and reduced neurogenesis. Other lines of research have found that obesity is associated with elevated levels of circulating peripheral β-amyloid, which can potentially compromise the integrity of the BBB.

These findings highlight the intricate interactions of multiple factors in the relationship between obesity and AD pathology. Moreover, exploring the interplay between obesity, AD and other components such as the GS and meningeal lymphatic system offers a promising avenue for a comprehensive understanding of the molecular basis and risk associations involved in these conditions.

Surprisingly, the observed patterns of brain atrophy in individuals with obesity did not all correlate with the distribution of amyloid plaques or tau proteins typically found in the brains of individuals with AD. Therefore, establishing a potential causality between obesity and AD requires further investigation, and it remains possible that neurodegeneration in obesity and AD are independent processes. These associations may thus simply reflect the higher prevalence of obesity and its associated cerebrovascular complications in AD populations. It is also plausible that the overlapping affected brain regions in obesity and AD correspond to areas that are inherently more vulnerable to atrophy in both conditions. This vulnerability could be attributed to higher energy demands in these specific brain regions, which may be further exacerbated by factors such as cerebrovascular compromise or IR, which can be observed in both diseases[172]. Therefore, future research in human studies is needed to fully comprehend the specific mechanisms underlying the increased risk of AD associated with obesity.

the circulation. Below the dura mater, the arachnoid mater is a thin avascular membrane. Portions of the arachnoid extend into the dura mater, forming a network that facilitates communication between the systemic venous system and the CSF. The innermost, thin layer, known as the pia mater, tightly adheres to the surface of the brain and spinal cord and hosts numerous blood vessels that supply the brain tissue with oxygen and nutrients. Surprisingly, a novel membrane called the subarachnoidal lymphatic-like membrane (SLYM) has recently been found between the arachnoid and pia maters in both mice and humans[40]. Although the SLYM exhibits selective permeability, allowing only very small molecules to pass, it harbours a local population of immune cells. Intriguingly, inflammation and ageing have been associated with increased concentration and diversity of immune cells at the SLYM. Rupturing the SLYM impairs both the CSF flow and the GS and permits the entry of non-CNS immune cells into the brain (Fig. 2). These studies, along with others, highlight the emerging understanding that the meninges serve as a site of early inflammatory processes in chronic neurological diseases, and the need to further investigate the role of the meninges in disease progression and develop therapeutic strategies aimed at maintaining their intactness to support better outcomes in neurological conditions (Box 3).

GS. The GS serves as a crucial brain-wide perivascular perfusion system, responsible for maintaining the brain's delicate extracellular environment. Its primary function is to efficiently clear waste products, soluble proteins and excessive ISF, while also regulating immunity and immune surveillance[41]. The proper functioning of the GS relies on the continuous transport of CSF across the brain parenchyma, which is primarily facilitated by astrocyte endfeet in contact with perivascular channels located in the choroid plexus. These astrocyte endfeet display a dense and polarized expression of aquaporin 4 (AQP4), a water channel typically found in ependymal–glial-limiting membranes. AQP4 has a crucial role in facilitating the rapid exchange of CSF and ISF, while it also regulates fluid flow within the ISF to effectively clear interstitial solutes from the brain parenchyma. The choroid plexus, lining the ventricles, is composed of a monolayer of epithelial cells interconnected by tight junctions. It acts as a crucial checkpoint, actively monitoring the brain for signs of infection and inflammation. The choroid plexus harbours a pool of immune cells, primarily macrophages, residing between the fenestrated vessels and the ependymal cells. This strategic positioning enables the choroid plexus to have a key role in regulating the entry of peripheral immune cells into the CNS, such as leukocytes. Moreover, this unique location renders the choroid plexus a potential trigger point for initiating neuroinflammation during pathological conditions[42–44].

The GS is not only important for waste clearance, but also ensures the exchange of non-waste products between CSF and ISF, such as glucose, lipids, amino acids and neurotransmitters, therefore contributing to the overall functionality of the brain. In a recent study, mice

https://doi.org/10.1038/s42255-024-01079-8

BOX 3

New discoveries: myeloid reservoirs for the brain in the skull and vertebral bone marrow

The recent implementation of tissue clearing has led to remarkable advancements in biomedical research, particularly in the field of neurobiology. By enabling the generation of highly detailed three-dimensional imaging of intact rodent organs and bodies, an intriguing discovery emerged: there are direct ossified vascular channels that connect skull and vertebral bone marrow to the meninges. These channels facilitate the trafficking of immune cells such as neutrophils during inflammation and serve as homeostatic myeloid reservoirs for both the meninges and the parenchyma[173]. The precise function of these putative channels in humans remains unknown and further research is needed to uncover how migratory myeloid cells are regulated within these channels under normal and inflammatory conditions, both in chronic and acute brain inflammation, and potentially in response to obesity (Fig. 2).

In healthy conditions, the skull provides the brain and meninges with a continuous supply of monocytes and neutrophils through direct dura–bone marrow connections. However, when injury or other neuropathological conditions cause an inflammatory state, these short vascular connections seem to have a critical role in mobilizing, recruiting and dispersing neutrophils into the CNS parenchyma. Research on the effects of inhibiting cell migration through these channels may present a novel mechanism for countering inflammation, as most prior research conducted on immune reactions in the CNS has focused on immune responses that originate in the CNS itself, particularly after a brain injury or stroke.

fed a long-term hypercaloric diet exhibited no significant differences in overall glymphatic inflow, except for an increase observed in the hypothalamus, which has, anatomically, facilitated access to the CSF content. This was accompanied by an augmentation in both astrocytic AQP4 vascular polarization and density[45]. The authors propose that the changes in the hypothalamic circuitry and neuroinflammation, associated with long-term high-fat diet feeding, enhance glymphatic clearance in the area. A report further suggested that GS impairments also occur in humans with obesity[46]. These recent studies raise some questions about the effect of a defective GS on brain health (Fig. 2). High levels of triglycerides in the blood, brain and CSF have been shown to reduce hypothalamic leptin and insulin signalling, leading to subsequent alterations in feeding behaviour and cognition[47]. Additionally, the influence of elevated cytokine levels on the GS remains an area requiring investigation. Further, it would be important to determine how elevated leptin levels affect the GS and whether the effects of high leptin extend beyond previously reported associations with microvascular beds and hypertension.

Hypothalamic dysfunction in obesity

Vascular interactions at the BBB interface

In the hypothalamus of both obese mice and humans with obesity, along with an increase in the number of degenerated endothelial cells, Yi and colleagues have uncovered an angiopathic phenotype, characterized by angiogenesis (microvasculature) that is reminiscent of diabetic retinopathy[48] (Fig. 3). These specific hypothalamic vascular changes occurring with obesity have been proposed to result from elevated circulating leptin levels, linked to a higher fat mass, as supported by studies on leptin-deficient obese mice, which are protected from these hypothalamic specific diet-induced alterations[49]. Besides, leptin has also been linked to the development of arterial hypertension in obesity[49], affecting the cardiovascular system primarily via the CNS, particularly by tuning sympathetic outflow from the hypothalamic and medullary pre-autonomic nuclei. These studies also provide intriguing evidence that vascularization is not uniformly affected by obesity across the entire brain, suggesting the presence of molecular and functional phenotypic variations along the vasculature, which could be influenced by the actual anatomical location, the metabolic characteristics or the specificity of immune responsiveness of circuits in different brain regions. This could confer varying levels of susceptibility or resilience to dietary factors, inflammation and diseases.

Hypothalamic neurons

It is important to note that not all brain areas are shielded by the BBB. The median eminence (ME), a circumventricular organ located at the base of the hypothalamus, is characterized by fenestrated capillaries, which have higher vascular permeability. Within the arcuate nucleus of the hypothalamus (ARC), adjacent to the ME, unique hypothalamic neurons reside that express agouti-related protein (AgRP). Remarkably, 60–70% of AgRP neurons are situated outside the BBB in the adult hypothalamus[50], which enables them to directly communicate with blood-borne metabolic signals, making them first-line responders in regulating eating behaviours based on the body's energy reserves. However, the absence of BBB protection renders these neurons particularly susceptible to peripheral inflammation and, therefore, to dysfunction[51]. Several studies have indicated that AgRP neurons exhibit early abnormal activation in response to the consumption of a hypercaloric diet, which persists despite elevated levels of leptin in the blood. Obesity and elevated dietary saturated fatty acids (SFAs) are associated with autophagy defects in AgRP neurons, which have an important role in promoting inflammation, contributing to acceleration of the obese phenotype[52,53] (Fig. 3). These findings support that the impulse to eat remains continuously active, resulting in a sustained state of excessive energy supply that may contribute to the development of hormone resistance and further storage of energy as fat, thus worsening obesity. Other studies suggest that prolonged exposure to a hypercaloric diet in mice promotes mitochondrial stress and apoptosis in the anorexigenic proopiomelanocortin (POMC) neurons, which are situated in direct proximity to AgRP neurons. This effect is attributed to increased levels of TNF produced by neighbouring microglial cells, contributing to the development of obesity[54–57] (Fig. 3). Recent discoveries have revealed that POMC neurons display functional and molecular heterogeneity[58], with the mechanistic target of rapamycin complex 1 signalling orchestrating the activity of distinct subpopulations variably in response to changes in energy availability to regulate feeding behaviour[59]. Emerging techniques such as single-cell spatial transcriptomics and patch-sequencing hold promise in answering unresolved questions. These include whether prolonged hypercaloric diet feeding or obesity induces functional impairments, including cell death, either in all POMC neurons, or in specific clusters of POMC neurons and associated glia, contributing distinctly to metabolic effects that participate in the obesity pathogenesis. Furthermore, such changes may vary depending on factors such as diet composition, duration of exposure, health status of the organism and/or history of obesity, among others.

Astrocytes

These are specialized glial cells that undergo rapid structural and functional rearrangements in response to stimuli in order to facilitate adaptative behaviours and processes both in the brain and eventually

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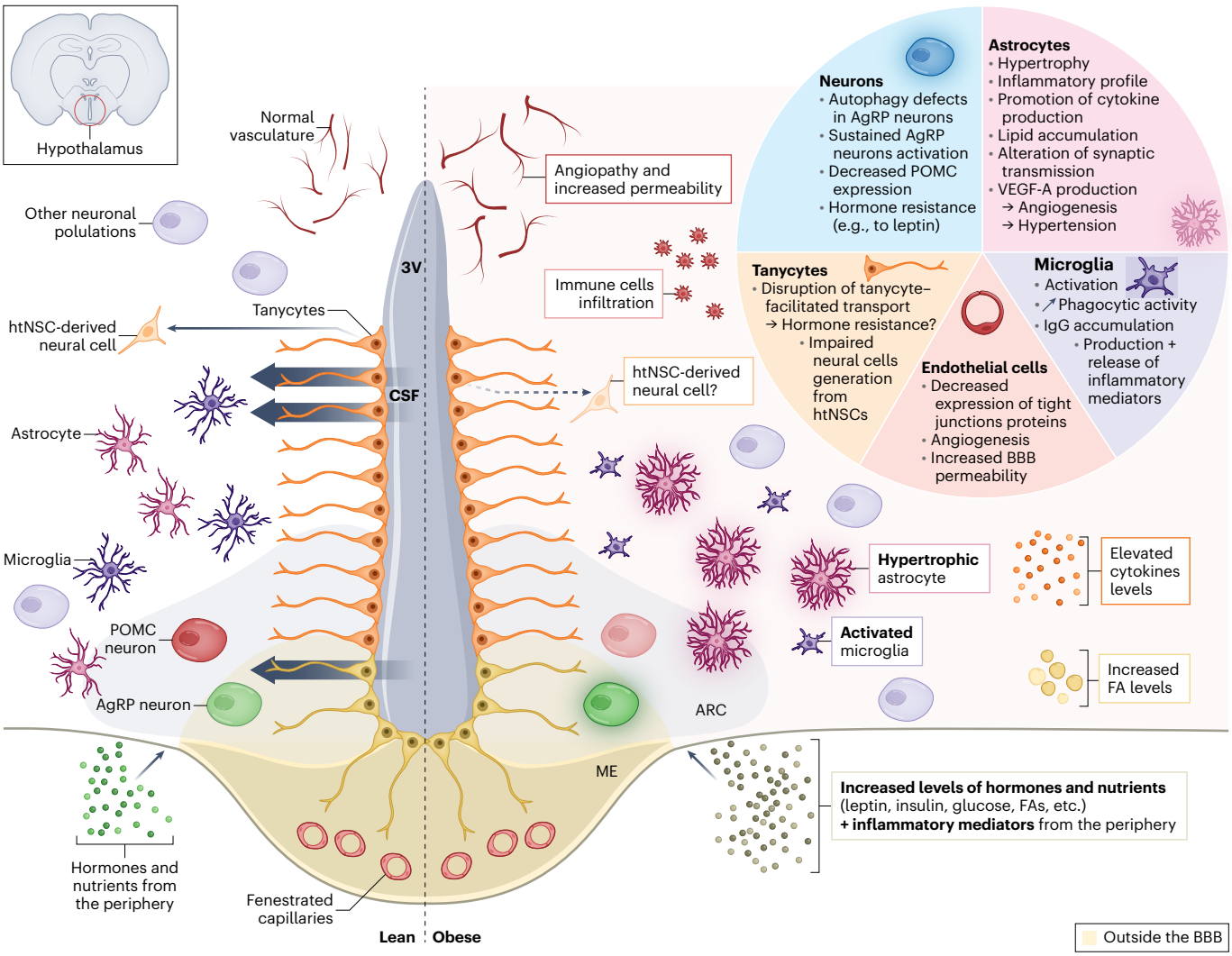

Fig. 3 | Obesity and hypothalamic dysfunction. Not all brain areas are shielded by the BBB (shown in yellow). The ME is a circumventricular organ located at the base of the hypothalamus, characterized by fenestrated capillaries with higher vascular permeability. Within the ARC, next to the ME, reside neurons that express the orexigenic AgRP or the anorexigenic POMC, regulating eating behaviours based on the body's energy reserves. Overall, the hypothalamus is particularly susceptible to peripheral inflammation and, therefore, to dysfunction. FAs, fatty acids.

the periphery. Astrocytes are closely associated with vascular beds and establish functional connections with neighbouring neurons via their intricate processes. Through physical contact and the release of soluble factors, astrocytes actively participate in the formation and remodelling of nearby blood vessels, and, in their distinct and well-defined territory, ensure precise control over the entry and/or sensing of nutrients, hormones and other metabolites from the circulation. Notably, hypothalamic astrocytes primarily display morphological and molecular changes in response to hypercaloric diets as they undergo cytoskeletal modifications characterized by dynamic changes in the expression of the glial fibrillary acidic protein (GFAP; Fig. 3). These changes are proposed to functionally affect energy homeostasis by inducing adaptive synaptic rearrangement and/or pathological modulation of neurotransmitter/ion homeostasis in surrounding neurons[56,60–62]. Several studies attribute this phenomenon to a distinct shift towards an inflammatory profile in astrocytes through an inhibitor of kappa B kinase beta/NF-κB-dependent mechanism, which contributes to sustained hypothalamic inflammation and heightened susceptibility to obesity development following a hypercaloric diet (Fig. 3). Notably, targeted reduction of inflammatory signalling in astrocytes under obesogenic conditions has been shown to protect mice from hypothalamic inflammation and glucose intolerance[63]. Similar studies have also indicated that astrocytes accumulate lipid droplets in fatty acid-enriched environments, as found in obesity (Fig. 3). These lipid-laden astrocytes promote the release of pro-inflammatory molecules, including IL-1β and IL-6, which can induce migration and activation of microglia and other surrounding cells, thereby intensifying hypothalamic inflammation[64]. Likewise, astrocyte functionality and inflammatory responses can be influenced by the surrounding reactive, activated microglia[65,66]. Most of these astrocytic changes have been attributed to the effect of circulating nutrients and hormones on these glial cells, promoting adaptations to maintain energy homeostasis via their complex interplay with the vasculature in the hypothalamus. It has been demonstrated that elevated circulating leptin levels found in hypercaloric diet-fed obese mice induce the production of VEGF-A in GFAP-expressing astrocytes in the hypothalamus, which promotes angiogenesis at the level of the microvasculature[49] (Fig. 3). Similar studies have also demonstrated that selectively removing leptin and insulin receptors in GFAP-expressing astrocytes of adult mice reduces the suppressive effects of leptin and glucose on food intake, respectively[67,68]. However, it is important to note that the functional effect of dietary factors in hypothalamic astrocytes can differ based on various

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BOX 4

The EGCs

The enteric glial cells (EGCs) are a type of peripheral glial cells situated in the enteric nervous system, actively involved in GI functions alongside enteric neurons. These glial cells resemble astrocytes in the brain, exhibiting an irregular, stellate shape and sharing molecular characteristics such as the expression of proteins such as GFAP and the calcium-binding protein S100β. They also possess receptors for neurotransmitters and neuromodulators, enabling them to respond to signals released by neurons[69]. This close physical interaction between enteric glia and neurons mirrors the relationship observed between astrocytes and neurons in the brain. Studies have shown that the loss or dysfunction of GFAP-positive cells from the ileum and jejunum of adult mice induces moderate local neuronal degeneration and a fulminating and fatal jejunoileitis, suggesting the importance of these cells in maintaining the integrity of the bowel[70]. Recent studies have also linked dysfunction of EGCs with neurodegenerative disorders such as PD. Given the similarities between EGCs and CNS astrocytes in their reactive nature, ability to modulate inflammation, exposure to dietary influences and potential involvement in neurodegenerative conditions such as PD, these cells may also have an active role in regulating gut–brain interaction in metabolic control. However, this area of research remains relatively under-explored, and further experiments are needed to fully understand their decisive role in obesity.

factors, which include the distribution of astrocytes across hypothalamic nuclei, the duration of obesity, the composition of the diet, the presence of inflammation, and even the ageing process. Singularly, some astrocyte-like glial cells have been identified outside the CNS, particularly in the gut (Box 4). Although their functions remain largely unexplored, these glial cells interact with enteric neurons, resembling astrocytes[69,70]. This suggests that they might have an important role, akin to astrocytes, in modulating gut–brain interactions relevant to metabolism regulation.

Tanycytes

These are a specialized type of ependymal cell that exhibit unique characteristics. Found along the wall of the third ventricle (3V), they serve both as a barrier and an interface regulating the entry of substances from the CSF, and through the less restrictive fenestrated vascular barrier surrounding the ME, where tanycytes also connect the hypothalamus to the pituitary portal blood system[71]. Indeed, depending on the nutritional state, through remodelling, dynamic structural rearrangements of tight junctions and the release of soluble factors, akin to astrocytes, tanycytes actively contribute to regulating the passage of relevant signals (for example, nutrients and hormones), from the bloodstream or CSF, to act on the brain circuits involved in metabolic regulation at the 3V level[19,71,72] (Fig. 3). However, unlike astrocytes, the plasticity mediated by tanycytes is highly regionalized. Tanycytes not only regulate the passage of substances but also can sense changes in the CSF levels of different types of metabolic substrates or metabolites such as glucose, amino acids and fatty acids, and engage signalling pathways, leading to circuits adaptations. Interestingly, it has also been shown that tanycytes can convert glucose to provide neurons with an energy substrate[71]. In recent years, a substantial body of research has underscored the pivotal role of tanycytes as highly sensitive shuttles for distributing blood-borne metabolic signals, including leptin and ghrelin, to precise brain regions responsible for regulating behaviour. It has been proposed that disruptions in the transport facilitated by tanycytes at the ME-barrier level are critical factors contributing to the development of hormone resistance in individuals with obesity[72–74] (Fig. 3). Furthermore, investigation into inhibiting the IKK–NF-κB pathway in tanycytes has shown their role in moderating IL-1β-induced anorexia, as evidenced by the alleviation of the latter following this blockade. This suggests that tanycytes serve as transporters for inflammatory factors from the periphery, mediating the effects of systemic inflammation in the brain[71,75].

Several studies have reported the presence of adult hypothalamic neural stem cells (htNSCs) predominantly located in the mediobasal hypothalamus[76–78], most of which are classified as tanycytes with dividing and self-renewing features. Indeed, various subtypes of tanycytes, such as α2 or β2, have been shown to have a crucial role as sources of new brain cells, including both neurons and glial cells. These tanycytes possess remarkable self-renewing abilities akin to those of adult htNSCs and express a repertoire of NSC markers such as nestin and transcription factors specific to hypothalamic proliferative cells. Interestingly, the proliferation rate of tanycytes and their progeny in response to hypercaloric feeding exhibits intriguing variations based on their specific locations and subtype. Specifically, research indicates the presence of a distinctive area known as the 'hypothalamic proliferative zone' within the ME. This zone exhibits increased cell proliferation, especially when exposed to an obesogenic diet, resulting in a greater population of neurons within this particular brain region[78]. Conversely, tanycytes and htNSCs that exhibit elevated levels of SOX2, a hallmark NSC marker, localized rather along the wall of the 3V, experience compromised survival and neurogenesis following prolonged exposure to hypercaloric conditions[55]. Reversing alterations in proliferation and differentiation observed under obesogenic conditions can be achieved effectively by reducing inflammation in the cellular environment[55]. These findings suggest that the inflammation emanating from the periphery, potentially particularly affect areas proximal to the 3V and ME, influencing the apparition or survival of newborn neural cells deriving from the NSCs within the hypothalamus, including neurons involved in the regulation of energy homeostasis (Fig. 3).

Microglia

These are referred to as parenchymal resident immune cells in the brain, serving as vigilant sentinels and among the first responders in immune modulation. In both rodent and human brains, microglial numbers remain constant throughout adulthood[79], with no substantial contribution from peripheral macrophages in the absence of pathological changes. With their processes continuously surveying their respective domains, microglia are prompt to adopt a reactive state and to respond to any form of insult via alterations in morphology and overall phenotype, marked by the production and release of inflammatory markers, as well as an enhanced phagocytic capacity (Fig. 3). However, microglial cells populate the brain in a region-specific manner, implying that different brain areas may not be equally affected by microglia-mediated responses associated with obesity. Nevertheless, the hypothalamus, which is widely recognized as a key area affected in obesity[56,80], has been extensively studied regarding the role of microglia in regulating whole-body energy metabolism. Interestingly, hypercaloric diet feeding, independent of leptin action or obesity itself, leads to the accumulation of IgG in the hypothalamic microglia, a phenomenon not observed elsewhere in the brain[57,81]. Microglia activation in the hypothalamus during obesity is largely dependent on the diet composition[82] and hormonal cues emanating from the periphery—rather than by adiposity itself (Fig. 3). Increased levels of SFAs have been suggested to be the primary trigger for microglial activation via a TLR4–NF-κB pathway, which can promote cell infiltration, food intake and inflammation[83,84]. The engagement of microglia and astrocytes into a pro-inflammatory programme by SFAs affects the entire local environment, including

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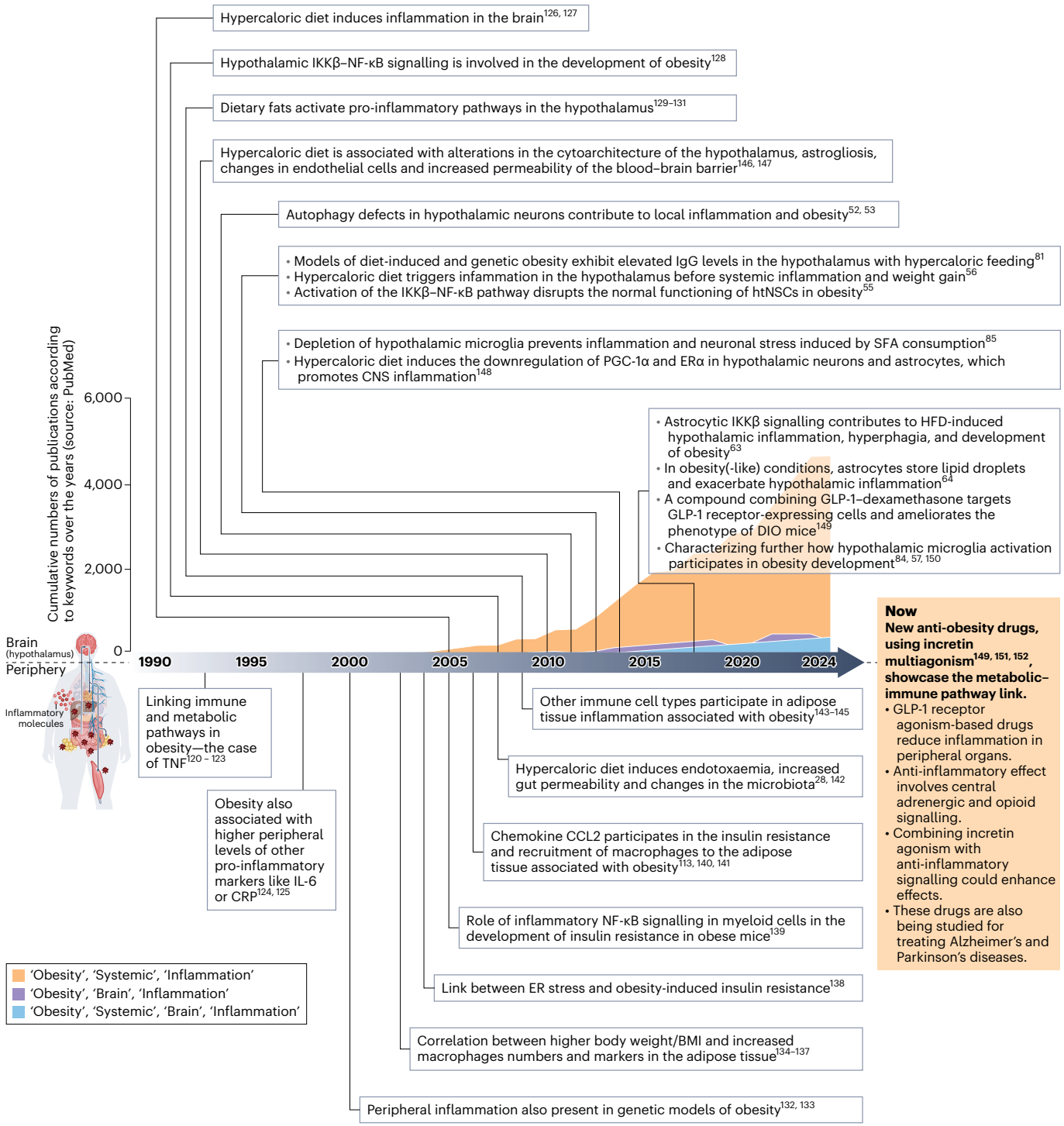

Fig. 4 | Timeline of key discoveries in the body–brain (hypothalamus) interactions and obesity-related inflammation. Landmark studies in the 1990s identified low-grade inflammation associated with obesity, notably in adipose tissue and throughout the periphery, marked by increased pro-inflammatory markers, immune cell infiltration and cellular stress. By the early 2000s, research began to elucidate the role of inflammation in obesity pathogenesis and associated conditions such as IR. Obesity was found to induce inflammation not only in the periphery but also within the brain, especially in the hypothalamus, prompting intensive investigation into central inflammation's origins and implications in obesity and its comorbidities[120–152]. Mechanisms include the effect of a high-fat diet on BBB permeability and inflammatory signalling in diverse cell types, disrupting central energy balance control and brain functions. Central inflammation induces local cellular stress and toxicity, and impairs hypothalamic stem cell neurogenesis. Ongoing research aims to understand the effects of obesity-associated inflammation on different brain cells, notably in neurodegenerative and cognitive disorders. The latest anti-obesity medications, based on incretin agonism, show promise in reducing inflammation both peripherally and in the brain, highlighting the complex interplay between metabolic and immune signalling pathways. CRP, C-reactive protein; ER, endoplasmic reticulum; ERα, oestrogen receptor alpha; HFD, high-fat diet; IgG, immunoglobulin G; IKKβ, inhibitor of kappa B kinase beta.

neuronal function and inflammation, given their primary roles[63,85]. Furthermore, depleting microglia from the hypothalamus of mice suppresses inflammation and alleviates neuronal stress resulting from excessive SFA consumption[85]. A recent study demonstrated that if obesity-associated hypothalamic gliosis seems to favour hyperphagia and weight gain, paradoxically, increased inflammatory signalling in microglia improves glucose tolerance independently of diet and weight in rodents. This phenomenon involves a TNF-dependent increase in hypothalamic glucose-sensing neurons (including POMC), which leads to a stronger first-phase insulin secretion[86].

Conclusion and futures perspectives

Over the past few decades, gradually accumulated evidence has consistently shown that obesity is associated with inflammation, affecting not only peripheral organs but also the brain. These interconnected phenomena compromise overall health and have a pivotal role in the pathogenesis of obesity (Fig. 4). Understanding the intricate mechanisms connecting obesity and persistent low-grade inflammation is vital for the development of new strategies to prevent disease and maintain overall health, including cognitive function. Additionally, we need better means than BMI to evaluate when excessive adiposity is affecting overall health due to effects on metabolism and the associated inflammatory response, as individuals have differing abilities to safely store fat. This idea has been reinforced by studies showing that the development of obesity-related health effects was predicted more by a history of lifelong body weight fluctuations and individual inflammatory states than BMI alone[87]. As our understanding of the complex mechanisms underlying obesity and inflammation improves, we are moving towards more precise and personalized therapeutic management. It is also crucial to recognize that not all individuals with obesity are necessarily unhealthy, and addressing social stigma is an important frontier for improving patients' mental and overall health.

Over the past decade, the field of obesity treatment has undergone a transformative shift following the discovery of a novel class of anti-obesity drugs, recently approved by the US Food and Drug Administration. Targeting multiple mechanisms simultaneously, the first generation of unimolecular incretin multi-agonists are approaching the efficacy of bariatric surgery in the treatment of T2D and obesity, and future iterations may surpass it[88–90]. These advancements represent a major step forward in treating obesity. Moreover, future directions focusing on maintaining a healthy weight after weight loss and minimizing weight fluctuations hold promise for a comprehensive approach to effectively managing obesity and its comorbidities in the near future, including in regard to cognition and dementia.

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Acknowledgements

We thank C. Holleman for comments. This research is supported by funding from the DZD, the German Research Foundation DFG under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy – ID 390857198), and Helmholtz Association - Initiative and Networking Fund. The funders had no role in decision to publish or prepare this work.

Author contributions

O.L.T. and C.G.-C. conceptualized the content, wrote, edited and revised the original draft. Both authors have reviewed and approved the final version of the manuscript for publication.

Competing interests

The authors declare no competing interests.

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Peer review information *Nature Metabolism* thanks Vincent Prevot and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Alfredo Giménez-Cassina, in collaboration with the *Nature Metabolism* team.