Astrocytes at the intersection of ageing, obesity, and neurodegeneration

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Abstract

Once considered passive cells of the central nervous system (CNS), glia are now known to actively maintain the CNS parenchyma; in recent years, the evidence for glial functions in CNS physiology and pathophysiology has only grown. Astrocytes, a heterogeneous group of glial cells, play key roles in regulating the metabolic and inflammatory landscape of the CNS and have emerged as potential therapeutic targets for a variety of disorders. This review will outline astrocyte functions in the CNS in healthy ageing, obesity, and neurodegeneration, with a focus on the inflammatory responses and mitochondrial function, and will address therapeutic outlooks.

List of abbreviations

Abbreviation	Full term
5X-FAD	Five-familial AD
ACC	Acetyl-coenzyme A carboxylase
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid
AMPK	Adenosine monophosphate-activated protein kinase
ANGPTL-4	Angiopoietin-like 4
ApoE	Apolipoprotein E
AQP4	Aquaporin 4
ATP	Adenosine triphosphate
Aβ	Amyloid beta
BAT	Brown adipose tissue
BBB	Blood-brain-barrier
BMI	Body mass index
C1qa	Complement component 1 subcomponent Q alpha polypeptide
Ca^{2+}	Calcium ion
CD36	Cluster of differentiation 36
CNS	Central nervous system
CREB	cAMP response element-binding protein
DAMP	Damage-associated molecular pattern(s)
DNA	Deoxyribonucleic acid
Drp1	Dynamin-related protein 1
DVC	Dorsal vagal complex
EAATs	Extracellular amino acid transporters
ECM	Extracellular matrix/matrices
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
Fis1	Fission protein 1
GABA	γ-aminobutyric acid
GFAP	Glial fibrillary acidic protein
GLUT1	Glucose transporter 1
GTP	Guanosine triphosphate
HFD	High fat diet
HFHSD	High-fat high-sucrose diet
Iba1	Ionized calcium-binding adapter molecule 1
IGF-1	Insulin-like growth factor 1
IKKβ	Inhibitor of kappa B kinase β
IL-1a	Interleukin 1a
IL-1β	Interleukin 1β
IL-6	Interleukin 6
IR	Insulin receptor
IRS1	Insulin receptor substrate 1
JAK-STAT	Janus kinase-signal transducer and activator of transcription

K$_{ATP}$	Potassium-sensitive ATP
KO	Knockout
MBH	Mediobasal hypothalamus
Mf1,2	Mitofusin 1,2
MIF	Macrophage migration inhibitory factor
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NFκB	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
NTS	Nucleus tractus solitarius; nucleus of the solitary tract
OB-R, LEP-R	Leptin receptor
Opa1	Optic atrophy 1
PD	Parkinson's disease
PGC-1α	Peroxisome-proliferator activated receptor gamma co-activator 1-alpha
PPARγ	Peroxisome-proliferator activated receptor gamma
Raf	Rapidly accelerated fibrosarcoma
ROS	Reactive oxygen species
SOCS	Suppressor of cytokine signalling
SOD1	Superoxide dismutase 1
STAT3	Signal transducer and activator of transcription 3
T2DM	Type 2 diabetes mellitus
TNF	Tumour necrosis factor
VEGF	Vascular endothelial growth factor
WAT	White adipose tissue

Introduction

The number of people with obesity is increasing, particularly in young people[1], presenting a global health and economic burden affecting more than 2 billion people worldwide[2]. In addition, cases of associated metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, and non-alcoholic fatty liver disease (NAFLD) have increased in the period from 2000 to 2019[3]. Obesity has profound effects on the whole body, including the central nervous system. As healthcare improves, and younger people with obesity age, this may expose added risk to age-related diseases with shared pathological mechanisms. Indeed, the global population as a whole is ageing, with estimates projecting that there will be 2 billion people over the age of 60 by the year 2050[4]. Ageing is the largest risk factor for neurodegenerative diseases which are similarly increasing, with estimates projecting that there will be ~14 million people in Europe with neurodegeneration by 2040[5]. Understanding the differences between a healthy ageing brain and what occurs during neurodegenerative disorders is essential to improving the limited therapeutic options for these debilitating diseases. Glia, non-neuronal cells of the nervous system, support brain function during health and disease. Despite pressures on maintaining energy balance, neuronal activity, and the immunologic state of the central nervous system, glia maintain homeostasis, underscoring the importance of these cells to maintaining cognitive function. Glial responses to environmental pressures (e.g. caloric surplus) and ageing are likely comprised of both protective and maladaptive responses. The purpose of this review is to summarise and explore the way glia intersect the disease pathologies of obesity and dementia. This review will discuss the molecular and cellular changes that occur as a result of obesity and compare them to healthy ageing to understand more about the relationship between obesity and neurodegeneration. Whilst glia serve pleiotropic roles in the brain, this review will focus primarily on astrocytes, the predominant glial cell type in the mammalian brain whose roles span all aspects of CNS function.

A brief glossary of terms

Throughout this review, the roles of astrocytes in the context of pathophysiological states will be discussed. While clinically relevant, this area of study has been subject to considerable debate and has historically suffered from a lack of clarity concerning astrocyte 'reactivity'. Attempts to delineate different astrocyte subtypes within specific pathological states have been misinterpreted as generalised astrocyte subtypes (for example, the A1/A2 nomenclature proposed by Liddelow *et al*. in the context of the specific responses of cortical forebrain astrocytes to neuroinflammation and ischaemia[6,7]). Indeed, recent evidence suggests that changes to astrocytes in pathological states occur on a spectrum, as a progressive transition[8]. Thus, the most recent consensus statement on astrocyte reactivity (for full details, readers are referred to Escartin *et al*.[8]) encourages a movement away from binary definitions and towards more appropriate nomenclature. Therefore, within this review we employ the recently-proposed definitions of astrocyte reactivity as "broadly equivalent to reactive astrogliosis… emphasising the capacity of astrocytes to adopt distinct state(s) in response to diverse pathologies"[8]. When used, in this review, "gliosis" also attempts to adhere to the definition laid out in the consensus statement ("the process whereby, in response to pathology, astrocytes engage in molecularly-defined programs involving changes in transcriptional regulation, as well as biochemical, morphological, metabolic, and physiological remodelling, which ultimately result in gain of new function(s) or loss or upregulation of homeostatic ones"[8]). In addition, our usage of "gliosis" may also refer to the loss of astrocyte morphological/functional plasticity, along similar lines to the hypothesis of glial asthenia[9], whereas we would add the caveat that astrocyte "reactivity", in contrast to "gliosis", is characterised by a *retention* of plasticity. Where used, "inflamed" refers to

the *generic*, uncharacterised, response of astrocytes to a non-specific inflammatory stimulus, which (rightly or wrongly) may or may not encompass stimulus-specific responses (i.e., a general theme that may be found within astrocyte responses to potentially damaging stimuli). When used, "pro-inflammatory" refers to stimuli associated with cellular/tissue damage that a) convey a damage signal throughout the cellular milieu and b) promotes the astrocyte to assume a pro-inflammatory response (regardless of whether this is temporarily or permanently), typically characterised by a metabolic shift towards glycolysis[10,11] and predominant secretion of pro-inflammatory cytokines (i.e. tumour necrosis factor, interleukin-6[10]), which may or may not encompass increased hypertrophy and loss of morphological complexity. Similarly, here we use the term "anti-inflammatory" in reference to an action opposing that of a pro-inflammatory stimulus, typically geared towards the resolution of damage/trauma/inflammation.

Glia: an overview

Glia have gained increasing appreciation in recent years as a heterogeneous class of cells which collectively support the nervous system from development to decline. Along with epithelial cells, glia form the blood-brain-barrier (BBB)[12–15] which facilitates the compartmentalisation of the CNS from the periphery. Due to their integral role in the BBB, glia dynamically control blood flow with regional specificity[14–16] in the brain in response to changes in energetic or nutrient requirements. Glia are also responsible for the inflammatory responses of the nervous system[17,18], detecting and responding to insults[19] and repairing damage, as well as preventing inappropriate access to the CNS by peripheral immune cells[20]. During development, glia are responsible for the myelination of neurons[21–23] and influence the formation of synapses[24–28], enabling rapid bidirectional communication across the brain and between the brain and the periphery. Thus, the scale of functions influenced by glial cells ranges from molecular to behavioural[29–31].

Broadly, glia can be divided into three 'classes' of cells, each working to fulfil the roles briefly described above. These are the astrocytes, oligodendrocytes, and microglia. Astrocytes and oligodendrocytes share a developmental lineage (being derived from radial glial cells[32]) and are commonly thought to differentiate from radial glial cells after neurogenesis has taken place. Despite their shared developmental lineage, oligodendrocytes and astrocytes serve distinct functions: generally speaking, oligodendrocytes myelinate neuronal axons[33]. In contrast, astrocytes are commonly thought to provide support for neurons[34,35] and are responsible for maintaining homeostasis in CNS tissue through various mechanisms[30,31]. Unlike astrocytes and oligodendrocytes, microglia do not differentiate from radial glial cells and instead differentiate along a similar lineage to peripheral macrophages. Around the time of neurogenesis (a phenomenon which predates astrocyte and oligodendrocyte differentiation[36,37]), microglial progenitor cells migrate into the developing neural tissue from the yolk sac prior to further differentiation and proliferation[26], thus populating the CNS as microglia. This distinction from the developmental lineage of astrocytes and oligodendrocytes likely belies the specialist function of microglia as the resident immune cells of the CNS: microglia are principally responsible for controlling the inflammatory response of the CNS and repairing damage[38] and, in concert with astrocytes, play a key role in synaptic pruning during CNS development[39]. The roles of astrocytes, which will be the focus of this review, are explored in finer detail below. For the purposes of this review, the term 'astrocytes' refers to the broad class also known as 'astroglial cells'[40], and not a particular subpopulation of astroglial cell.

Astrocytes

Astrocytes are a group of heterogenous glial cells, typically of a stellate morphology, intimately involved with maintaining CNS homeostasis[41–43]. In conjunction with pericytes and vascular

endothelial cells, astrocytes are part of the BBB. Astrocytic endfeet line the BBB and regulate the uptake of nutrients from the blood; they express transporter proteins such as glucose transporter 1 (GLUT1)[44,45], fatty acid binding proteins[46,47], and apolipoprotein E (ApoE)[48–51], enabling the uptake of glucose and fats into the CNS to control CNS energy balance and substrate supply. This is facilitated by a close relationship between astrocytes and neurons, wherein a single astrocyte can extend structures termed 'fine processes' to interact with multiple neurons[52–54]. Thus, astrocytes are readily positioned to sense and respond to neurotransmission and associated neuronal demands via fine processes and the expression of receptors such as extracellular amino acid transporters (EAATs)[55] in addition to various neurotransmitter receptors (such as α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid [AMPA][56], N-methyl-D-aspartate [NMDA][57–59] and γ-aminobutyric acid [GABA][60] receptors), and potassium-sensitive ATP (K_{ATP}) channels[61]. Astrocytes, along with oligodendrocytes and microglia, modulate neural activity through the release of molecules known as 'gliotransmitters'. Gliotransmitters include molecules such as lactate[62–66] and ATP[67,68], and amino acids such as D-serine and glutamate[69]. These molecules have recently gained attention for facilitating interglial communication in addition to the arguably better recognised hemichannel-facilitated Ca^{2+} waves[70] more traditionally associated with interglial communication[71–73]. Alongside secretion of gliotransmitters, astrocytes are also responsible for the secretion and maintenance of the CNS extracellular matrix via the secretion of glycoproteins such as laminins[74], collagens[75], hyaluronic acid[76], in addition to matrix metalloproteinases[77,78] providing an important contribution to preserving and modulating CNS tissue integrity.

Beyond these functions, in concert with microglia, astrocytes also participate in the resolution of CNS injury, trauma, or inflammation as part of their homeostatic functions. To facilitate this, astrocytes express a variety of cytokine[79–81] and chemokine[82] receptors. Like microglia, astrocytes are highly plastic cells and can adopt a variety of morphologies in response to stimuli; indeed, the true extent of astrocyte heterogeneity is an emerging field and may have relevance to pathological states as recently evidenced[19,83–85]. There is evidence to suggest that astrocyte morphology may underlie a functional 'priming'[86–88], i.e., biasing an astrocyte towards one function over others, and that future study of astrocytes may require further sub-categorisation of glial cell populations that are not yet fully defined. Astrocyte function can also be impacted by pathological conditions, such as brain inflammation, which has been linked to astrocyte reactivity[19,89,90] and altered ECM secretion[91–93]. A similar increase in astrocyte reactivity has been observed in age-associated pathologies such as Alzheimer's disease[94,95] and other neurodegenerative conditions[96,97]. In obesity a similar process occurs, beginning with the insidious accumulation of low levels of pro-inflammatory signalling molecules (such as tumour necrosis factor (TNF)[98,99], interleukin 1β (IL-1β)[98], macrophage migration inhibitory factor (MIF)[98,99] and IL-6[99] [for review see Ellulu et al. 2017[99]]), which gradually begin to promote CNS inflammation. Because astrocytes are part of the BBB, they are exposed to these noxious stimuli before the rest of the brain in early, prodromal disease stages and respond to the gradually increasing pro-inflammatory signals, which has been linked to a deterioration of astrocyte function, increased astrocyte activation, and subsequent cognitive decline associated with obesity[100].

In this review and beyond

The focus of this review will be the intrinsic changes to astrocyte biology from the perspectives of normal healthy ageing, neurodegeneration, and obesity. The mechanistic overlap between each state will be compared and the differentiating factors from the literature identified. Other glia such as oligodendrocytes and microglia play critical roles in these processes and may have as much bearing as astrocytes on these outcomes. Where possible, the roles of these cells in relation to astrocyte functionality under these conditions will be acknowledged, but for a more extensive

review of microglia and oligodendrocyte functions readers are referred to Li and Barres[101] (microglia) and Simons and Nave[102] (oligodendrocytes).

Mechanistic factors at the intersection of glia, nutrition, obesity, and ageing

Inflammation

Astrocyte inflammatory responses

Though it is not considered their primary function, astrocytes have an arsenal of inflammatory responses to preserve the integrity of the CNS parenchyma. Expressing receptors for damage-associated molecular patterns (DAMPs)[103], astrocytes can detect and respond to inflammatory signalling within the CNS to maintain homeostasis. This is achieved by secretion of pro-inflammatory cytokines such as TNF and IL1β (which may be induced by DAMP receptor signalling or by reactive microglia[19]) and results in changes to astrocyte function, morphology, and phenotype[18,43,104]. Notably, following exposure to pro-inflammatory stimuli, astrocytes generally increase expression of glial fibrillary acid protein (GFAP)[90,105,106]. Acutely, the astrocyte response to inflammation is accompanied by a shift in the metabolic phenotype of astrocytes, upregulating glycolysis in a nuclear factor kappa B (NFκB)-dependent manner[107], whereas prolonged inflammatory responses increase mitochondrial oxidative phosphorylation[107] and add to intracellular reactive oxygen species (ROS) generation[108].

Astrocyte inflammatory responses in healthy ageing

Evidence suggests that ageing modulates astrocyte functionality: in 2018, Boisvert et al.[109] used an aged mouse model (4 months vs 2 years of age) to demonstrate that astrocytes in the aged mouse showed upregulation of various inflammation-associated genes across the brain, including *Gfap*, *Serpina3n* (a serine protease of the Serpin superfamily) and *C4b* (a member of the complement cascade involved with synaptic pruning), suggesting that aged astrocytes show increased reactivity and may contribute to age-associated cognitive decline by degrading synapses. The authors further showed that, in the cerebellum, aged astrocytes expressed greater levels of genes associated with a pro-inflammatory state such as *caspase-1*, *caspase-12*, *Cxcl5*, and toll-like receptors[109], which have similar functions to DAMPs. In a separate study, Clarke et al.[110] demonstrated that aged mouse astrocytes showed increased expression of the complement pathway genes *C3* and *C4b*, the chemokine *Cxcl10*, as well as *Serpina3n* and genes associated with antigen presentation such as *H2-K1*, which the authors interpreted as markers of increased astrocyte reactivity in the aged model. Most of the observed astrocyte reactivity was induced by pro-inflammatory cytokines (IL-1a, TNF, C1qa[19]) secreted by pro-inflammatory microglia present in the aged brain – though this failed to account for enhanced *Serpina3n* levels, which remained enhanced even in aged astrocytes isolated from IL-1a, TNF, and C1qa triple-knockout (KO) mice[110] suggesting that other mechanisms may be at play.

In addition, Pan et al.[111] have shown that aged (12 month) mice compared to young (2 month) mice exhibited increased expression of genes such as *C4b* and *Serpina3n* in addition to downregulation of genes such as *Gpr17* (involved in sensing damage to myelin sheaths) and *Tnr* (linked to neuronal adhesion, neurite outgrowth, and synaptic plasticity)[111]. This suggests that aged astrocytes adopt a phenotype which may compromise their ability to support neuronal and synaptic integrity. While

intriguing, the data presented by Pan *et al.* and Boisvert *et al.* are applicable only to male mice; moving forward, it would be highly beneficial to explore changes to astrocyte reactivity in a mixed sex cohort of mice and determine any sexual dimorphism therein. Indeed, sexually dimorphic responses have been recorded in peripheral immune cells, suggesting that a similar mechanism may be at play in the brain[112,113].

Alongside this, Gatto *et al.* have shown that astrocytes directly converted from human fibroblasts retain hallmarks of ageing (e.g. telomere length and mRNA expression of telomerases) and show a dysregulated inflammatory response to IL-1β and increased nuclear translocation of NFκB[114]. However, the cellular functions regulated by NFκB go beyond inflammatory responses and are generally accepted as including proliferation and metabolism[107,115–117]. If the findings from Gatto *et al.* are confirmed, this may signify that loss of NFκB regulation in astrocytes may lead to prolonged activation of inflammatory signalling pathways from these cells. Tight control of the inflammatory response of the CNS is critical to maintaining structural integrity and cognitive functioning, as inflamed astrocytes struggle to provide homeostatic support to the CNS[12,118]. Thus, one may speculate that aged astrocytes are subject to impedance of intrinsic homeostatic mechanisms that may underlie the reduced astrocyte functionality observed in studies of ageing.

Considered together, the existing literature suggests that aged astrocytes adopt pro-inflammatory phenotypes which may be detrimental for neuronal survival and which contribute to cognitive decline observed in healthy ageing.

Astrocyte inflammatory responses during obesity

Obesity is a condition characterised by excessive fat accumulation. This fat is largely stored in the periphery, typically in white adipose tissue, resulting in chronic low-grade inflammation[119]. This inflammation originates in the adipose tissue, increasing over time and culminating in systemic inflammation[119]. The increased levels of circulating pro-inflammatory cytokines released during obesity are detected by the CNS, promoting a reactive phenotype in astrocytes and microglia, leading to the loss of CNS homeostasis[19,84,106,118,120,121]. Astrocytes express a range of receptors for cytokines and chemokines[79–82], as well as nutrient sensors (e.g., GLUT1[45,107,122], ApoE[48–50,123,124]) and hormonal receptors (leptin, oestrogen[125]). This allows astrocytes to integrate and respond to changes in energy balance and inflammation, which are both altered in obesity. As mentioned, pro-inflammatory signalling molecules are secreted by the peripheral immune system and detected by astrocytes, leading to increased astrocyte reactivity[106,120]. This drives further release of CNS-originating pro-inflammatory signals from microglia and has been linked to impaired functioning of oligodendrocytes, contributing to demyelination and cognitive impairment[126].

Via magnetic resonance imaging (MRI), Kullmann *et al.*[127] demonstrated that male and female participants with greater accumulation of visceral fat displayed increased water content in the hypothalamus, an area of the CNS critical for maintaining homeostasis and regulating food intake. This may be due to increased astrocyte reactivity, which has been shown to modulate expression of aquaporin-4 (AQP4). AQP4 is expressed on astrocyte endfeet (which help form the BBB) and is used to draw water from the blood into the CNS. Via genetic ablation of AQP4, murine studies have demonstrated that AQP4 is involved in memory formation[128], and astrocytic AQP4 expression is regulated via the NFκB pathway, as recently demonstrated in a recent study by Lu *et al*[129]. In this study, mouse primary astrocytes were treated with TNF for 6h, resulting in increased cell volume (implying increased water uptake); intriguingly, AQP4 expression increased from as little as 3h treatment with TNF, and pharmacological blockade of NFκB signalling attenuated AQP4 expression in response to TNF[129]. Because the homeostatic capabilities of astrocytes are impaired during

chronic inflammation, this may represent a potential mechanism by which altered astrocyte reactivity induced by obesity contributes to changes in brain water content and may partially explain the cognitive deficits associated with obesity. However, it must be noted that other glial cells almost certainly play a role in the manifestation of these phenotypes and that this observation likely cannot be attributed to astrocytes alone.

Further evidence for the role of astrocyte inflammation during obesity can be drawn from rodent studies. For example, previous evidence from Buckman *et al*. has shown that chronic high fat diet (HFD) administered for 20 weeks increases GFAP immunoreactivity in the hypothalami of obese mice[106], implying an increase in astrocyte reactivity. Similarly, Popov *et al.* showed that in young (2 months) mice, one month of HFD is sufficient to induce enlargement of hippocampal astrocytes without an increase in GFAP expression[130]. This was accompanied by increased glutamate uptake, which Popov *et al.* interpreted as a metabolic shift in astrocytes[130]. In these young mice, provision of HFD improved long-term potentiation (a marker of improved memory formation) and reduced anxiety-like behaviours as measured in the open field test[130]. However, there are fundamental differences between these studies: the work of Buckman *et al*. focussed on changes to the hypothalamus, a region of the CNS involved that plays a critical role in regulating homeostasis and energy intake, whereas the work of Popov *et al*. focussed exclusively on the hippocampus, an area of the brain associated with memory formation. Together these studies suggest that there may be regional differences in the astrocyte response to inflammatory stimuli which perhaps reflects recent advancements in our understanding of astrocyte heterogeneity. Crucially, Popov *et al*. used animals younger (2 months) than those in the work of Buckman *et al*. (3-4 months) – and, as shown by Pan *et al*.[111], astrocytes in 4-month-old mice have a different age-related transcriptome, and presumably behavioural phenotype, to 2-month-old mice. The work of Buckman *et al*. is also supported by a study from Douglass *et al*.[131], which demonstrated that genetic ablation of inhibitor of kappa B kinase β (IKKβ), a regulator of NFκB activation, attenuated the inflammatory phenotype of astrocytes in response to HFD. Furthermore, in 2017 Balland *et al*.[132] demonstrated that 10 days of HFD was sufficient to alter astrocyte morphology and upregulate GFAP immunoreactivity in the arcuate nucleus of the hypothalamus (a hypothalamic region concerned with regulating hunger and satiety signalling), which showed a similar level of both GFAP immunoreactivity and signal transducer and activator of transcription 3 (STAT3) activity (measured by phosphorylated STAT3 expression) to mice exposed to HFD for 20 weeks. Taken together, these data suggest that obesity may have age- and region-dependent effects on astrocyte reactivity within the CNS. Ultimately, regardless of potential transient benefits to cognition, prolonged exposure to an obesogenic diet has been linked to reduced cognitive performance in diverse populations of humans[133–135]. This is likely mediated, at least in part, by increased astrocyte reactivity in response to the peripheral inflammation associated with obesity which likely impairs the homeostatic properties of astrocytes.

Mitochondrial dysfunction

Astrocyte mitochondrial dysfunction

Contrary to historical perspective, mitochondria are not just the energy-producing units of cells; they are now understood to have complex functions linked to a variety of cellular processes. For example, mitochondria are closely involved with the production of ROS, which serve a variety of functions in cellular inflammatory responses and ageing[108,136–138]. Furthermore, mitochondria are understood to have complex interactions with other organelles – they can undergo fusion or fission with other mitochondria in response to the energetic requirements of cells[139] and form close associations with other organelles[140] to facilitate the supply of ATP required for proper organelle function.

As cells tightly involved with regulating energy use and nutrient uptake within the CNS, and which provide trophic support to neurons, conservation of proper mitochondrial function is important to maintain astrocyte functionality. Indeed, mitochondrial dysfunction in astrocytes has been linked to the development of Parkinson's disease[141] and is linked to a loss of motility in astrocyte cilia[142]. Moreover, repeated exposure to environmental pollutants, such as titanium dioxide, is associated with reduced mitochondrial functionality and glutamate uptake in primary astrocytes[143], highlighting the importance of mitochondrial functionality in maintaining astrocyte functionality.

Astrocyte mitochondrial dysfunction in healthy ageing

Though a causal relationship has yet to be ascertained, ageing is associated with systemic chronic low-grade inflammation and increased astrocyte reactivity[110], resulting in metabolic dysregulation in astrocytes, an increase in mitochondrial ROS production, and oxidative stress. The work of Gatto *et al.*[114] demonstrated that, in addition to dysregulation of the astrocyte inflammatory response discussed above, induced astrocytes from aged donors were less able to regulate ROS levels – likely due to lower superoxide dismutase 1 (SOD1) expression. This may translate to increased astrogliosis during ageing and a reduction of the ability of astrocytes to meet their homeostatic requirements. This is supported by the findings of Pan *et al.*[111], who demonstrated that genes associated with mitochondrial complex, membrane, and matrix formation were downregulated in aged astrocytes, suggestive of impaired mitochondrial biogenesis and integrity.

Senescent astrocytes, induced by hydrogen peroxide, are less able to support neurons in a co-culture model compared to non-senescent astrocytes[144]. Astrocytes can shuttle mitochondria to neurons to preserve or restore neuronal functioning following CNS trauma or inflammation[145]. Whilst this was initially studied in the context of ischaemia, these findings may also extend to ageing. For example, using a direct co-culture model, Morales-Rosales *et al.* recently showed that aged astrocytes reduced the mitochondrial membrane potential of neurons, which in turn exhibited greater oxidation[144]. Impaired mitochondrial function is a key source of oxidative stress in neurons[146], thus it is plausible that intercellular mitochondrial transfer from astrocytes to neurons explains the observations from Morales-Rosales *et al.*: the experimental model allows the formation of direct intercellular connections, thereby facilitating the exchange of cellular contents (e.g., mitochondria[145], vesicles[147]).

In a murine model of neurodevelopment, peroxisome-proliferator activated receptor gamma co-activator 1-alpha (PGC-1α) expression has been linked to mitochondrial development and the functional maturation of astrocytes in synapse formation in mice aged 1-7 weeks[148]. Downregulation of PGC-1α via conditional KO impaired astrocyte proliferation and maturation, resulting in a less complex cellular morphology, and in an earlier study PGC-1α deficiency was linked to increased body fat accumulation in mice[149]. In the periphery, PGC-1α expression is reduced during ageing (for review see Vernier *et al.*[150]) and has been linked to the development of Parkinson's disease[151]. Aged mice show reduced retinal PGC-1α expression, and in human primary astrocytes enhanced PGC-1α signalling has been shown to protect against oxidative stress[152]; thus, the clinical potential of PGC-1α likely extends beyond applications to neurodegenerative conditions. Restoration of mitochondrial function in astrocytes via enhancement of PGC-1α expression in aged astrocytes may represent a tangible therapeutic target to reverse the cognitive decline associated with healthy ageing by restoring mitochondrial functionality in astrocytes.

Together, these studies highlight the importance of proper mitochondrial functions in astrocytes and the contribution of aberrant astrocytic mitochondrial function to the loss of CNS homeostasis and

integrity observed in ageing, mediated at least in part by increased astrogliosis in the aged brain, doubtless contributing to the mild cognitive decline observed in healthy ageing.

Astrocyte mitochondrial dysfunction during obesity

Mitochondria are highly dynamic organelles, adapting in response to cellular state via processes termed 'fission' (i.e., division) and 'fusion' (i.e., the merging of distinct mitochondria into a single mitochondrion). These dynamics are governed by a set of GTPases: mitochondrial fusion is regulated by optic atrophy 1 (Opa1) and mitofusins 1 and 2 (Mf1, Mf2) which govern inner and outer mitochondrial membrane fusion, respectively. In contrast, mitochondrial fission is regulated by dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1). During obesity, mitochondrial dynamics become impaired and have been linked to these proteins[153–156] (for review of mitochondrial fission and fusion dynamics in obesity, see references[154–156]). Mitochondrial fission:fusion ratios are linked to the energetic states of cells[157–159], and mitochondrial functions in astrocytes during obesity have been subject to recent attention. A study from Filippi et al.[160] showed that HFD exposure increased mitochondrial fission within the dorsal vagal complex (DVC; a region of the brainstem). Because astrocytes have been linked to regulation of feeding behaviours, this may represent a therapeutic target for managing obesity. However, this study did not explore the effects of Drp1 inhibition on the cognition of HFD mice. Given that mid-life obesity may associate with cognitive decline[161–163], hypothetically, Drp1 inhibition would ameliorate these effects. Exploring this hypothesis throughout the age of the rodents may also prove beneficial for exploring the longitudinal effects of Drp1 inhibition as a therapeutic intervention, and would allow the interplay between obesity, timeliness of interventions, and cognitive decline during ageing to be further explored. On the other hand, there is evidence from a range of ethnic backgrounds to suggest that obesity may not affect cognitive decline in healthy ageing[164], so it is plausible that Drp1 inhibition may have no effect on cognition in obese rodents. Regardless, it is evident that mitochondrial function in astrocytes plays a key role in regulating bodyweight and food intake.

Recent research from Fozzato et al.[165] followed up on the earlier work of Filippi et al.[160] and instead focused on the nucleus of the solitary tract (NTS; a region of the DVC) in HFD-fed rats, showing that 2-week HFD exposure is sufficient to reduce glucose uptake in peripheral brown adipose tissue (BAT; measured via ^{18}F-fluorodeoxyglucose uptake). Importantly, astrocyte-specific inhibition of Drp1 via adenoviral transfection partially attenuated this phenotype and partially restored glucose sensitivity in BAT, though this effect did not translate to white adipose tissue (WAT). Moreover, NTS astrocyte-specific inhibition of Drp1 prevented large fat droplet accumulation in BAT. Rats with astrocyte-specific Drp1 inhibition also showed reductions in enzymes involved with lipolysis (adipose triglyceride lipase, hormone-sensitive lipase) and increased cluster of differentiation 36 (CD36) expression, a receptor for long-chain fatty acids. In contrast, overexpression of Drp1 in NTS astrocytes reduced BAT innervation and expression of CD36s[165]. This reinforces the link between mitochondrial dynamics and metabolic substrate utilisation, and more widely emphasises the role of astrocytes in facilitating CNS-periphery communication.

Complementing this, work from Varela et al. has shown that the availability of metabolic substrates to astrocytes is also linked to obesity[166]. The authors reported enhanced fatty acid availability (confirmed by lipoprotein lyase activity) in multiple brain regions and increased phosphorylation of adenosine monophosphate-activated protein kinase (AMPK; signifying activation of AMPK) and acetyl-coenzyme A carboxylase (ACC; signifying inactivation of ACC) in the mediobasal hypothalamus, inferring enhanced fatty acid oxidation, in a tamoxifen-inducible angiopoietin-like 4 (ANGPTL-4) KO in hypothalamic astrocytes[166]. The authors also reported that mitochondria in ANGPTL-4-deficient hypothalamic astrocytes were unchanged following exposure to HFD, unlike in

wild-type controls. Together, these data suggested a phenotype protected from HFD-induced obesity. In contrast, conditional deletion of peroxisome proliferator-activated receptor gamma (PPARγ, which is regulated by ANGPTL-4) had the reverse effect and increased the likelihood of HFD-induced obesity in mice[166]. Following HFD exposure, PPARγ-deficient hypothalamic astrocytes showed increased reactivity and hypertrophic mitochondria versus wild-type mice also exposed to HFD, in addition to significantly greater bodyweight gain, food intake, and reduced physical activity, implying greater susceptibility to HFD-induced obesity[166]. It would be intriguing to see how the phenotype of aged mice with either PPARγ-or ANGPTL-4-deficient astrocytes respond to HFD, which presents a potential avenue for future research. Regardless, promotors of astrocytic PPARγ and ANGPTL-4 may hold promise as therapeutic targets for metabolic disorders. Unfortunately, changes to the expression of Opa1, Mfn1/2, Drp1 or Fis1 were not addressed by this research. Based on the observed phenotypes, one may predict altered activity or expression of these GTPases, but experimental evidence of this would be beneficial and could complement the study in aged mice. Importantly, both PPARγ and PGC-1α regulate mitochondrial biogenesis[167] and the NFκB pathway[168,169]; therefore, modulation of this signalling cascade may present a promising therapeutic target for suppressing mitochondrial dysfunction during obesity.

Together, these data highlight the critical role astrocyte mitochondrial fragmentation plays in susceptibility to obesity. Given that obesity may play either a neuroprotective or neurodegenerative role in healthy ageing, further research is clearly needed to better understand the nature of obesity throughout an individual's lifespan in the context of a diverse and fluctuating genetic and phenotypic environment to draw conclusions on the net effects for CNS health.

Regulation of bodyweight by astrocytes

As explored above, obesity and ageing have similar effects on astrocytes, notably by promoting astrocyte reactivity and mitochondrial dysfunction. In addition to being affected by obesity and ageing, astrocytes may also drive these processes by influencing nutritional intake throughout an individual's lifespan. As key regulators of food intake, the contribution of these astrocytes to bodyweight-associated disorders may represent a key therapeutic target for refining treatment strategies for disorders associated with dysregulation of these processes.

Obesity

Obesity has detrimental effects on astrocytes ranging beyond the promotion of astrocyte reactivity and mitochondrial dysfunction. Notably, astrocytes express receptors for the hormone leptin. Under normal conditions, leptin is released by adipocytes and its signalling mediates satiety and decreases food intake via neurons in the arcuate nucleus of the hypothalamus. This includes neuropeptide Y and agouti-related peptide neurons as well as astrocyte-mediated leptin signalling, which regulate neuronal transmission in the hippocampus[170]. Moreover, obesity has been associated with increased leptin receptor expression in hypothalamic astrocytes[171–173], and Jayaram *et al.* showed that astrocyte-specific leptin receptor deficiency ameliorates the effects of leptin resistance in obese mice[174]. Together, these studies suggest that astrocytes play a crucial role in regulating bodyweight via the leptin pathway. Furthermore, leptin is associated with pro-inflammatory cytokine release from hypothalamic astrocytes[175,176], mediating feeding behaviour[177–179]. Although Jayaram *et al.*[174] did not examine cytokine secretion from leptin receptor-deficient astrocytes, one may anticipate that this would be reduced during obesity. This is because leptin stimulates pro-inflammatory cytokine release via the activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway[180–183], which drives the secretion of various pro-inflammatory signalling molecules. Furthermore, leptin resistance is a hallmark of various neurodegenerative

conditions which is well recapitulated by animal models[184–186], and may contribute to neuroinflammation via chronic activation of the JAK-STAT pathway. Alongside leptin resistance, obesity is associated with resistance to insulin. Insulin, released from pancreatic β-cells in response to high plasma glucose levels, and also locally within the CNS from the choroid plexus, acts on many cells including astrocytes to regulate glucose uptake[187]. Prolonged exposure to insulin promotes insulin resistance in astrocytes and results in reduced expression of insulin receptors on these cells. In line with this, insulin-receptor KO astrocytes (a model of insulin resistance) show reduced glucose uptake and increased ROS production[188], alongside reduced mitochondrial respiration, and reduced mitochondrial DNA[189]. This suggests that insulin-resistant astrocytes may provide poorer trophic support to the CNS parenchyma. Importantly, recent evidence suggests that insulin resistance in the brain is mediated by increased astrocyte reactivity and inflammatory signalling[190], highlighting the complex interplay between these processes and suggesting a mechanism by which insulin resistance may contribute to cognitive decline in obesity. However, the contribution of insulin resistance to the onset of CNS pathophysiology in the context of neuroinflammation remains unclear. Thus, when considered together these data provide an intriguing potential therapeutic angle for the treatment of obesity and management of associated neuroinflammation, which may influence food intake and contribute to weight gain.

Frailty

Frailty is a hallmark of ageing associated with marked loss of tissue, particularly adipose and muscle tissue, and is linked to age-related reductions in physical activity[191–193]. While frailty is associated with neurodegenerative conditions, it is important to emphasise that it also forms a part of normal ageing that is not associated with specific pathologies[192,193]. In contrast with obesity, frailty is associated with low leptin levels which correlate with poorer health outcomes[194]. Frailty is also associated with leptin resistance[195–198] possibly linked to greater adiposity in earlier life[199,200]. Additionally, frailty is characterised by increased levels of circulating pro-inflammatory cytokines[195,201–203]. This likely reflects an inflamed environment within the CNS parenchyma[118], possibly contributing to a reduced ability of astrocytes as homeostatic and energy-sensing units. Elevated leptin in earlier life, and the associated increases in pro-inflammatory cytokine secretion and glial reactivity, may thus contribute to cognitive decline. Moreover, one may postulate that the subsequent effects of enhanced leptin levels and leptin resistance on feeding behaviours may predispose individuals to the development of frailty as key homeostatic mechanisms fail. This is potentially typified by the detrimental effects of enhanced cytokine secretion on hypothalamic function and the hypothalamic-pituitary-adrenal axis, alongside disrupted functionality of feeding-associated signalling molecules such as insulin-like growth factor 1 (IGF-1)[204–206]. Likewise, insulin resistance is associated with frailty[207], and disruption of the IGF-1 pathway in astrocytes under oxidative stress was recently shown to impair neuronal support[208], potentially suggesting that disrupted insulin signalling during frailty may contribute to age-related cognitive decline. Importantly, insulin resistance increases circulating insulin levels, which contributes to continued activation of inflammatory signalling mechanisms such as the JAK-STAT and NFκB pathways[209] and may contribute to increased astrocyte reactivity during ageing. A cascade of events may, therefore, impede the homeostatic functions of astrocytes that are key for the regulation of food intake, thus contributing to frailty in later life.

Contributions of obesity to cognitive decline and neurodegeneration at the level of the astrocyte

Ageing is the largest risk factor for the two most prevalent neurodegenerative disorders, Alzheimer's disease (AD) and Parkinson's disease (PD)[210]. Similarly, obesity also contributes to neurodegeneration and cognitive decline[211,212], and even in young people (aged 12-35 years) obesity negatively correlates with cognitive performance[213,214]. However, it is unclear what drives the relationship between impaired cognition and obesity. Despite this, it is known that episodic memory impairments are associated with higher body mass index (BMI), and it is thought that this aspect of memory is particularly relevant for appetite control[215–217]. Furthermore, higher cognitive scores are predictive of weight loss following bariatric surgery[218,219], further underscoring the notion that cognition influences bodyweight regulation. Moreover, deliberate weight loss has a low order improvement on cognition[220] indicating that obesity causes at least some cognitive impairment. Taken together, these studies suggest that there may be a bidirectional relationship between obesity and cognitive impairment.

In addition to cognitive impairment, people with obesity also have grey matter brain atrophy patterns that closely resemble that in AD[221], and mid-life obesity is associated with an increased risk of AD[222–224], further reinforcing the link between bodyweight and CNS health. Obesity shortens life expectancy, however, improvements in healthcare provision suggest that the detrimental effects of obesity on life expectancy will be mitigated in the near future. Thus, as rates of obesity increase and the population ages, neurodegeneration may occur at an increased rate. The exact mechanisms by which obesity contributes to cognitive impairment are not well established and would benefit from further research. However, obesity has several effects on glial function that may relate to neurodegenerative risk, which are explored further below.

Inflammation

The peripheral inflammation marker c-reactive peptide is increased in people with obesity[214,225] and levels of inflammation and oxidative stress in the CNS are increased by high fat diets[226–230]. At a cellular level this can be observed as elevated gliosis: GFAP and Iba1 (a microglial marker) levels are elevated in mice fed a HFD for 8 weeks compared to chow-fed mice[231]. In humans, there are also an increased number of Iba1-positive cells in the hypothalami of people with a BMI greater than 30 compared to a BMI below 25[231], demonstrating that this relationship is conserved. Mechanistically, the inflammatory response of astrocytes is required for diet-induced obesity and hypothalamic inflammation in mice as evidenced in 2017 by Douglass *et al*[131]. This study used an inducible IKKβ KO mouse model to demonstrate that GFAP-positive cell ramification was decreased in response to HFD exposure (with no change in cell number), with decreased hypothalamic expression of cytokine genes *Il1b* and *Il6*[131]. Furthermore, *Npy* (an orexigenic signal) was significantly lowered and *Bdnf* (an anorexigenic signal) significantly increased by suppressing GFAP-cell NFκB signalling[131]. These changes occurred without changes to the ramification or number of microglial cells or the expression of key microglial cytokine genes *Tnfa* and *Ccl2*[131].

Inflammation also increases AQP4[129] as discussed earlier, and changes to hypothalamic water balance have also been described in obesity[127]. Similarly, aquaporin dysregulation occurs in both AD and PD, amyotrophic lateral sclerosis (ALS), and traumatic brain injury among other CNS conditions[232–234]. Crucially, in the CNS, AQP4 is exclusively expressed in astrocytes[232] and is particularly relevant for glymphatic clearance of waste products (e.g. protein aggregates) from this

region[234]. As obesity alters AQP4 expression and increases CNS water, particularly in the hypothalamus[127], indicating impaired glymphatic action, it is plausible that this coincides with impaired CNS-waste clearance thus increasing pathological accumulation of amyloid-β (Aβ) and other proteins.

A key regulator of cellular inflammatory responses is the NFκB signalling pathway[115,209,235]. Alongside their key roles in regulating mitochondrial biogenesis, PPARγ and PGC-1α have emerged as key regulators of NFκB signalling[167] which highlights the multifaceted functionality of NFκB signalling and the various modalities which influence activation of this pathway[107,115,209,235]. Poor expression of PPARγ and PGC-1α in the periphery correlates with increased inflammation[167], suggesting that a similar mechanism might underlie or correlate with prolonged neuroinflammation. This likely correlates with altered mitochondrial metabolism observed during chronic neuroinflammation, where the brain parenchyma develops a predominantly glycolytic profile without the subsequent elevations in mitochondrial respiration one would anticipate following the proper resolution of the inflammatory response.

Considered together these studies show that astrocytic inflammatory signalling is required for central inflammation and propagating obesogenic signalling, and highlight that HFD and obesity synergistically create a pro-inflammatory environment in the brain parenchyma which is well established to contribute to central inflammation. Chronic exposure to inflammatory stimuli and re-activation of pro-inflammatory signalling pathways ultimately culminates in impairment of astrocyte functionality, contributing to gradual cognitive decline throughout an individual's lifespan (Figure 1). Loss of CNS homeostasis is also posited as a major contributing factor to the onset of neurodegeneration, with many of the facets of CNS impairment in obesity being mirrored in these pathologies.

Astrocyte-BBB dysregulation in neurodegeneration

The BBB regulates the transfer of molecules between the brain and periphery. In AD and obesity, the integrity of the BBB is impaired, meaning that the CNS is infiltrated by peripheral cells and inflammatory molecules. As a key brain region heavily involved with energy homeostasis, the hypothalamus is closely linked with the BBB, thus changes to BBB permeability are noted to affect this area. A region of the hypothalamus, the mediobasal hypothalamus (MBH, found close to the third ventricle) is known to be subject to gliosis following HFD exposure as discussed above[106,130,132]. Moreover, a high-fat high-sucrose diet (HFHSD) induces angiogenic processes in the MBH, increasing blood vessel length and density, and concomitantly reducing in BBB integrity in mice[236]. Importantly this hypothalamic vascular remodelling also occurs in both rodents and humans with type 2 diabetes[237,238]. Separate work from Paula et al. demonstrated that, within 48 hours of HFD exposure, the permeability of the murine BBB transiently increases before returning to normal[239]. However, this study also reported that following one and four weeks' HFD exposure, BBB permeability significantly increases[239]. Together these findings are indicative of complex temporal control of BBB dynamics in response to hypercaloric diets, which potentially warrants further investigation. As mentioned above, astrocytes form part of the BBB and regulate the 'neurovascular unit', a complex multicellular macrostructure comprised of neurons, astrocytes, pericytes and blood vessel endothelial cells. Astrogliosis in the hippocampus[239] and hypothalamus[236] is elevated after several weeks of HFD and HFHSD, respectively, indicating a chronic role for astrocytes in regulating and responding to high caloric intake. Separate work has shown that, acutely, hypothalamic mouse astrocytes in vivo have elevated morphological complexity and GFAP immunoreactivity 24 hours after HFD induction[240]. Thus, while astrocytes react to caloric excesses induced via both HFD and

HFHSD, the potential mechanisms by which astrocytes alter BBB permeability in response to these stimuli have yet to be fully elucidated. It has been touted that this may be due in part to increased astrocytic release of vascular endothelial growth factor (VEGF), increasing hypothalamic angiogenesis[236] potentially detrimentally. Conversely, in AD, low VEGF levels are associated with disease severity[241], and VEGF supports neuronal survival and neurogenesis[242], suggesting that, in AD pathology, reduced angiogenic potential contributes to cognitive decline. Together, this suggests that astrocytic VEGF signalling, which is altered by both obesity and AD, needs strict regulation in a brain region-dependent manner and complicates therapeutic efforts aimed at modulating this pathway. Additionally, the anti-inflammatory TNF monoclonal antibody infliximab decreases HFD-induced BBB permeability[239]. While microglia are the primary immune cell in the brain, astrocytes are also capable of secreting and responding to TNF[243–246]. Astrocytes are more closely linked to regulation of BBB function than microglia, so hypothetically the BBB response to HFD is regulated by astrocytic inflammatory signalling over multiple time scales and may act as a tangible therapeutic target.

Hormonal dysregulation

Beyond directly indicating nutrient levels in the body, leptin and insulin contribute to neuronal health and synaptic plasticity and memory[247,248]. Both leptin and insulin levels are chronically elevated in long-term obesity, and hormone resistance can occur which may contribute to impaired synaptic plasticity[249–251]. Mechanistically, it is unclear how hormone resistance occurs, but inflammatory signalling (TNF, IL-1β, and MIF) can directly cause insulin and leptin resistance[98]. Components of the leptin signalling pathway such as suppressor of cytokine signalling (SOCS) proteins, ER-stress, and NFκB, are all reported to contribute to insulin resistance[98]. Hyperleptinaemia caused by obesity also impairs BBB integrity via VEGF-mediated angiogenesis without complete coverage of tight junction presence, which is integral to BBB control of permeability[236]. Furthermore, in obesity, leptin receptor expression on hypothalamic astrocytes[189] is elevated which may exacerbate leptin-mediated and inflammation-mediated insulin resistance. Additionally, Aβ can impair astrocyte insulin signalling in primary mouse astrocytes[189], indicating that there may be a positive feedback loop between impaired metabolic signalling and worsening Aβ accumulation leading to further impairments of metabolic function and so on.

As discussed previously, obesity causes a chronic pro-inflammatory state throughout the whole body, including in the CNS, with profound impacts on astrocyte functionality. This extends to hormonal sensing – HFD exposure in mice impairs insulin signalling via insulin receptor (IR), IR-substrate 1 (IRS1) and Ras/Raf/ERK signalling pathways, decreases glucose transporter presence at the cell membrane (potentially impairing glucose uptake), and reduces ERK/CREB signalling, which could all contribute to the observed impairments to long term potentiation[252] and thus advance the pathology of AD. Brain glucose uptake is partly dependent on intact astrocytic insulin receptor signalling, as IR deficiency in several astrocyte subtypes has been shown to impair glucose uptake[253]. Furthermore, in AD and T2DM, cognitive function and brain connectivity are associated with reduced insulin action in the brain[254]. In the 5xFAD mouse model of AD (containing five AD-linked mutations), loss of insulin signalling in astrocytes exacerbates the AD-like phenotype[189]. Moreover, intranasal insulin therapy may improve memory and mood in people with AD, though mixed effects have been reported from larger scale clinical trials of this method[255]. Nonetheless, these bodies of evidence strongly suggest that promotion of insulin signalling in the CNS may ameliorate cognitive decline, or at the very least, serve as a potential adjunct therapy for AD pathology. Conversely, other studies suggest that disrupting insulin/IGF1 signalling may improve cognitive healthspan. For example, in 1993, Kenyon *et al.* demonstrated that a disruptive mutation to Daf-2 (an IGF-1 receptor homologue)

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in the nematode *Caenorhabditis elegans* increases longevity two-fold[256]. Moreover, using drosophila, in 2017 Augustin *et al*. showed that the disruption of insulin signalling both systemically and in central neural circuits prevents age-related decline and increases life expectancy[257]. In contrast to the bodies of evidence above, together these studies suggest that, at least in invertebrates, targeted disruption of insulin signalling may have beneficial effects on cognition. In agreement with this, studies in human cells[258] and mouse models of AD[259–262] suggest that disruption of the insulin/IGF1 signalling pathways improves outcomes and suggest that whilst insulin therapies may serve as a therapeutic intervention for neurodegenerative conditions, further study is required to understand the potential effects of modulating insulin signalling in the CNS prior to clinical adoption. Indeed, despite the potential benefits of disrupting insulin signalling to ameliorating cognitive decline, multiple studies indicate that disrupted insulin signalling in human pathologies is detrimental to health. For example, promoting insulin signalling via the sensitiser metformin is a first-line treatment for T2DM[263–265], a disorder characterised by loss of insulin sensitivity[266]. One potential explanation for these conflicting data may be that the insulin and IGF signalling pathways serve functionally distinct purposes across developmental stages and locations, such as in the brain and peripherally[267–269]. For example, insulin signalling is important for proper organismal development[270–272], suggesting that the *timeliness*, *dose*, and *duration* of insulin signalling may be key. It is a false dichotomy to categorise insulin/IGF1 signalling as "good" or "bad"; instead, there is likely an optimal amount of signalling that is at neither end of a spectrum[273]. Proper consideration of the potential role of insulin signalling in neurodegenerative pathologies and the history of the patient is likely to crucial to proper clinical employment of insulin modulation for the management of cognitive decline during ageing.

Another important metabolism-regulating hormone is leptin. Astrocytes express leptin receptors (OB-R, LEP-R) in the various brain regions (for review see McGuire *et al*.[274]), and conditional KO of OB-R in astrocytes prevents leptin-induced decreases in feeding and decreases astrocytic association with neural feeding circuits[275]. In opposition to frailty, as discussed previously, in healthy ageing leptin levels correlate with preservation of cognitive function[276]. Furthermore, in AD transgenic mice (Tg2576 and ApoE4), there are normal leptin levels but impaired leptin signalling[277]. Leptin signalling resistance is also inducible in primary astrocytes *in vitro* exposed to amyloid-β1-42[277]. Together, this suggests that the disruption of that astrocytic hormonal sensing and signalling as seen in obesity mirrors that observed in AD and potentially other neurodegenerative conditions, and therefore likely contributes to their progression.

Thus, the functions of insulin and leptin signalling during normal physiology are relatively well understood in the processes of regulating energy balance. Moreover, roles in memory formation are emerging for these proteins, highlighting the multifaceted nature of these potent signalling pathways. However, there are knowledge gaps in the understanding of how their dysregulation occurs or how this contributes to neurodegeneration. It is well established that glucose hypometabolism is a pathological hallmark of several neurodegenerative disorders, and there is some evidence showing a negative correlation between body mass index and cerebral glucose metabolism[278,279]. One may hypothesise that these are connected to the changes in the homeostatic roles of insulin and leptin in energy balance. While it is known that astrocytes respond and contribute to integration of hormonal signals, their intrinsic changes in obesity and neurodegeneration require further exploration to facilitate their therapeutic modulation.

Conclusions

Astrocytes and other glia, long overshadowed by neurons, have emerged as central players in maintaining CNS homeostasis, and with multifaceted functions ranging from regulating blood flow to modulating CNS inflammatory responses and synaptic integrity. In the context of healthy ageing, astrocytes respond to the accumulation of insoluble plaques and changes in CNS tissue by adapting their metabolic and inflammatory profiles to support neural maintenance, energy supply, neurotransmission, and maintenance of the BBB. Obesity has profound effects on the CNS at structural and signalling level. Elevated inflammatory and altered energy states impair astrocyte-neuron communication and metabolic substrate exchange. This review presents evidence that the changes caused by obesity may advance brain ageing in part by impacting astrocyte function. For example, in neurodegeneration, appropriate inflammatory responses are impaired (glial paralysis[118] and bystander injury at different disease stages) which overlap with obesity-mediated chronic low-grade inflammation. Secondly, the metabolic and mitochondrial changes caused by obesity may contribute to the immunometabolic context that accelerates neurogenerative processes. The literature shows that chronic inflammation occurring from excessive fat accumulation and circulating hormone levels in obesity, and toxic protein aggregates in neurodegeneration, contribute to cognitive impairment beyond normal decline in healthy ageing. What differentiates obesity and neurodegeneration is the source of inflammatory stimuli; in neurodegeneration these can also include environmental pollutants and immune responses to infiltrating pathogens (Figure 1). Regardless, the overlapping signalling responses between these apparently distinct pathways may contribute to the development of the other. One aspect which remains unclear is the balance between impaired glucose metabolism in the brains of people with obesity and/or neurodegeneration and the increased demand for glycolysis as a part of mounting robust glial inflammatory responses. What, then, distinguishes neuroinflammation in healthy ageing from that observed in obesity or neurodegenerative conditions? While similar mechanisms are observed across all three states, and thus noxious stimuli may accumulate in the brain parenchyma during healthy ageing, current evidence suggests that (unlike during CNS pathologies or metabolic disorders) inflammatory responses are able to reach the important resolutory phase and thus prevent the chronic immunometabolic stress of the CNS that is associated with obesity and neurodegenerative conditions (Figure 1).

Thus, this review underscores the roles of astrocytes in obesity and neurodegenerative pathologies and the complexity of changes therein (Figure 1). While these conditions have a complex web of pathological mechanisms, the presence of astrocytes in so many strands of these webs suggests that astrotherapeutics may facilitate profound changes to the pathology onset or procession. While there are significant limitations to implementing this into clinical practice, progress has been made at the level of basic research to better understand key astrocyte functions and more precisely identify astrocytic subpopulations.

Data availability statement
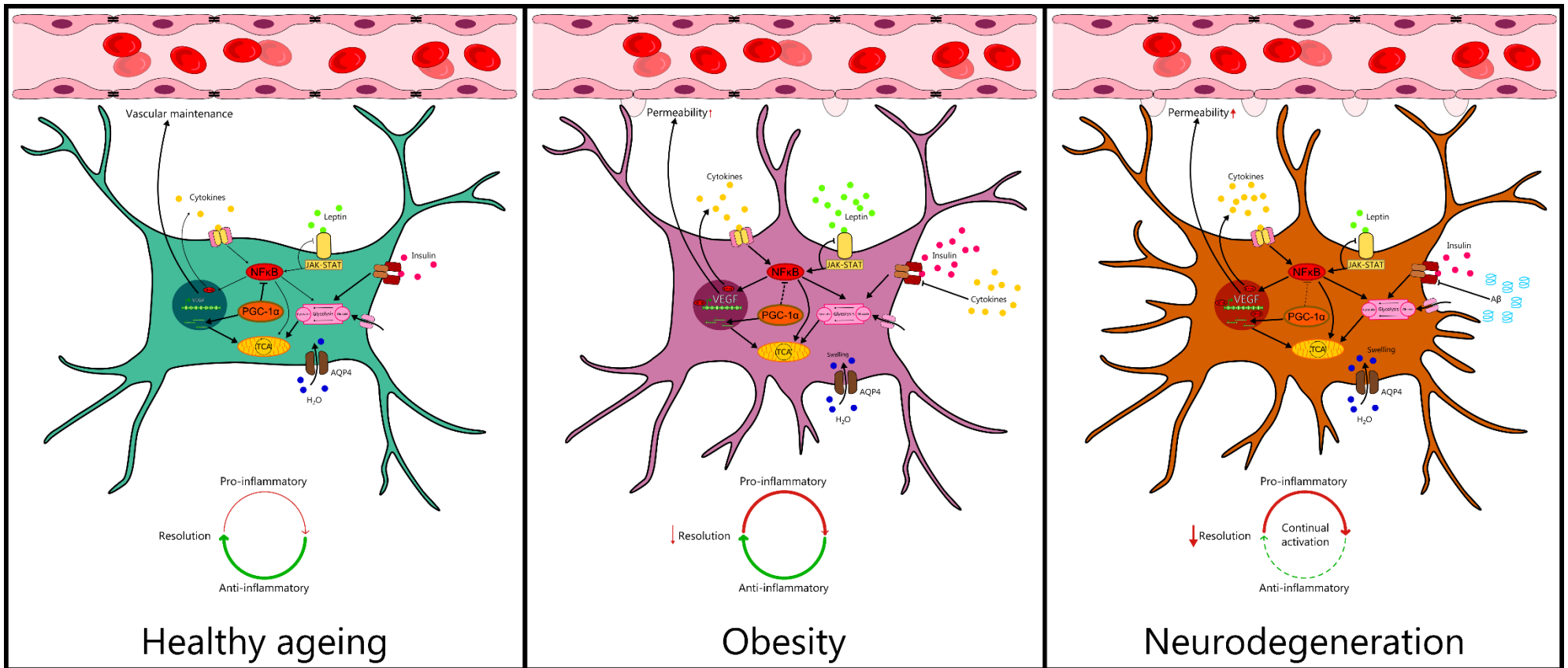
There is no applicable data to share.

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Figure 1. Astrocytic signalling during healthy ageing, obesity, and neurodegeneration.

Healthy ageing: inflammatory signalling is proportionate and anti-inflammatory processes result in resolution to noxious stimuli mediated by nuclear factor kappa B (NFκB). Thus, cytokine signalling is at normal levels. The brain and astrocytes are metabolically active and reliant on glycolysis and mitochondrial respiration. Hormonal signalling such as leptin and insulin is proportionate to energy balance with intact receptor sensitivity. Blood brain barrier (BBB) integrity is normal. Glymphatic activity via aquaporin 4 (AQP4) is appropriate. **Obesity:** elevated levels of pro-inflammatory cytokines and NFκB signalling result in an increase in glycolytic activity, astrocyte hypertrophy and ramification, leptin and insulin receptor insensitivity, and VEGF levels increase causing inappropriate angiogenesis and impaired BBB integrity. AQP4 activity is increased causing cell swelling and water accumulation. The chronic inflammatory stimuli lead to incomplete resolution of the inflammatory cycle. **Neurodegeneration:** cytokine levels are further elevated which exacerbates the aforementioned NFκB signalling outcomes. While leptin levels are typically lower than in obesity, the outcome is similar in that there is low functional leptin signalling. Insulin resistance also occurs partly mediated by cytokine activity and amyloid-β (Aβ). This impairs insulin-mediated glucose uptake and glycolytic activity. While NFκB signalling is high during neurodegeneration, increasing glycolysis, it is unclear how this

integrates with cerebral glucose hypometabolism. Ultimately, pro-inflammatory processes dominate the anti-inflammatory/repair process leading to incomplete resolution of noxious stimuli.

References

1. Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q, et al. Trends in obesity prevalence by race and hispanic origin - 1999-2000 to 2017-2018. JAMA - Journal of the American Medical Association. 2020;324(12):1208–10. doi: 10.1001/jama.2020.14590

2. Smith KB, Smith MS. Obesity Statistics. Primary Care - Clinics in Office Practice. 2016;43(1):121–35. doi: 10.1016/j.pop.2015.10.001

3. Chew NWS, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, et al. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metab. 2023;35(3):414-428.e3. doi: 10.1016/j.cmet.2023.02.003

4. Organisation WH. Ageing and health [Internet]. [cited 2023 Nov 15].

5. Tomaskova H, Kuhnova J, Cimler R, Dolezal O, Kuca K. Prediction of population with Alzheimer's disease in the European Union using a system dynamics model. Neuropsychiatr Dis Treat. 2016;12:1589–98. doi: 10.2147/NDT.S107969

6. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature Publishing Group [Internet]. 2017;541(7638):481–7. doi: 10.1038/nature21029

7. Liddelow SA, Barres BA. Reactive Astrocytes: Production, Function, and Therapeutic Potential. Immunity [Internet]. 2017;46(6):957–67. doi: 10.1016/j.immuni.2017.06.006

8. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions [Internet]. Vol. 24, Nature Neuroscience. Nature Research; 2021 [cited 2021 Jun 3]. p. 312–25. doi: 10.1038/s41593-020-00783-4

9. Verkhratsky A, Marutle A, Rodríguez-Arellano JJ, Nordberg A. Glial Asthenia and Functional Paralysis: A New Perspective on Neurodegeneration and Alzheimers Disease. Neuroscientist. 2015;21(5):552–68. doi: 10.1177/1073858414547132

10. Robb JL, Hammad NA, Weightman Potter PG, Chilton JK, Beall C, Ellacott KLJ. The metabolic response to inflammation in astrocytes is regulated by nuclear factor-kappa B signaling. Glia. 2020;68(11):2246–63. doi: 10.1002/glia.23835

11. Chen Z, Yuan Z, Yang S, Zhu Y, Xue M, Zhang J, et al. Brain Energy Metabolism: Astrocytes in Neurodegenerative Diseases. CNS Neurosci Ther. 2023;29(1):24–36. doi: 10.1111/cns.13982

12. Cabezas R, Ávila M, Gonzalez J, El-Bachá RS, Báez E, García-Segura LM, et al. Astrocytic modulation of blood brain barrier: Perspectives on Parkinson's disease. Front Cell Neurosci. 2014;8(AUG):1–11. doi: 10.3389/fncel.2014.00211

13. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006;7(1):41–53. doi: 10.1038/nrn1824

14.	Li Z, McConnell HL, Stackhouse TL, Pike MM, Zhang W, Mishra A. Increased 20-HETE Signaling Suppresses Capillary Neurovascular Coupling After Ischemic Stroke in Regions Beyond the Infarct. Front Cell Neurosci. 2021;15(November):1–15. doi: 10.3389/fncel.2021.762843

15.	Díaz-Castro B, Robel S, Mishra A. Astrocyte Endfeet in Brain Function and Pathology: Open Questions. Annu Rev Neurosci. 2023;46:101–21. doi: 10.1146/annurev-neuro-091922-031205

16.	Mishra A, Reynolds JP, Chen Y, Gourine A V., Rusakov DA, Attwell D. Astrocytes mediate neurovascular signaling to capillary pericytes but not to arterioles. Nat Neurosci. 2016;19(12):1619–27. doi: 10.1038/nn.4428

17.	Yang Q qiao, Zhou J wei. Neuroinflammation in the central nervous system: Symphony of glial cells. Glia. 2019;67(6):1017–35. doi: 10.1002/glia.23571

18.	Giovannoni F, Quintana FJ. The Role of Astrocytes in CNS Inflammation. Trends Immunol. 2020;41(9):805–19. doi: 10.1016/j.it.2020.07.007

19.	Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature Publishing Group. 2017;541(7638):481–7. doi: 10.1038/nature21029

20.	Muldoon LL, Alvarez JI, Begley DJ, Boado RJ, Del Zoppo GJ, Doolittle ND, et al. Immunologic privilege in the central nervous system and the blood-brain barrier. Journal of Cerebral Blood Flow and Metabolism. 2013;33(1):13–21. doi: 10.1038/jcbfm.2012.153

21.	Rasband MN, Peles E. The nodes of Ranvier: Molecular assembly and maintenance. Cold Spring Harb Perspect Biol. 2016;8(3):1–16. doi: 10.1101/cshperspect.a020495

22.	Almeida RG, Pan S, Cole KLH, Williamson JM, Early JJ, Czopka T, et al. Myelination of Neuronal Cell Bodies when Myelin Supply Exceeds Axonal Demand. Current Biology. 2018;28(8):1296-1305.e5. doi: 10.1016/j.cub.2018.02.068

23.	Hughes AN, Appel B. Oligodendrocytes express synaptic proteins that modulate myelin sheath formation. Nat Commun. 2019;10(1):1–15. doi: 10.1038/s41467-019-12059-y

24.	Schiweck J, Eickholt BJ, Murk K. Important shapeshifter: Mechanisms allowing astrocytes to respond to the changing nervous system during development, injury and disease. Front Cell Neurosci. 2018;12(August):1–17. doi: 10.3389/fncel.2018.00261

25.	Um JW. Roles of glial cells in sculpting inhibitory synapses and neural circuits. Front Mol Neurosci. 2017;10(November):1–8. doi: 10.3389/fnmol.2017.00381

26.	Ginhoux F, Lim S, Hoeffel G, Low D, Huber T. Origin and differentiation of microglia. Front Cell Neurosci. 2013;7(MAR):1–14. doi: 10.3389/fncel.2013.00045

27.	Pfrieger FW. Roles of glial cells in synapse development. Cellular and Molecular Life Sciences. 2009;66(13):2037–47. doi: 10.1007/s00018-009-0005-7

28. Ebrahimi M, Yamamoto Y, Sharifi K, Kida H, Kagawa Y, Yasumoto Y, et al. Astrocyte-expressed FABP7 regulates dendritic morphology and excitatory synaptic function of cortical neurons. Glia. 2016;64(1):48–62. doi: 10.1002/glia.22902

29. Chen N, Sugihara H, Kim J, Fu Z, Barak B, Sur M, et al. Direct modulation of GFAP-expressing glia in the arcuate nucleus bi-directionally regulates feeding. Elife. 2016;5(OCTOBER2016):1–21. doi: 10.7554/eLife.18716

30. Piirainen S, Chithanathan K, Bisht K, Piirsalu M, Savage JC, Tremblay ME, et al. Microglia contribute to social behavioral adaptation to chronic stress. Glia. 2021;69(10):2459–73. doi: 10.1002/glia.24053

31. Damulewicz M, Doktór B, Baster Z, Pyza E. The Role of Glia Clocks in the Regulation of Sleep in Drosophila melanogaster. Journal of Neuroscience. 2022;42(36):6848–60. doi: 10.1523/JNEUROSCI.2340-21.2022

32. Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci. 2009;32:149–84. doi: 10.1146/annurev.neuro.051508.135600

33. Gerhards R, Pfeffer LK, Lorenz J, Starost L, Nowack L, Thaler FS, et al. Oligodendrocyte myelin glycoprotein as a novel target for pathogenic autoimmunity in the CNS. Acta Neuropathol Commun. 2020;8(1):1–17. doi: 10.1186/s40478-020-01086-2

34. Ricci G, Volpi L, Pasquali L, Petrozzi L, Siciliano G. Astrocyte-neuron interactions in neurological disorders. J Biol Phys. 2009;35(4):317–36. doi: 10.1007/s10867-009-9157-9

35. Rama Rao K V., Kielian T. Neuron-astrocyte interactions in neurodegenerative diseases: Role of neuroinflammation. Clin Exp Neuroimmunol. 2015;6(3):245–63. doi: 10.1111/cen3.12237

36. Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci. 2009;32:149–84. doi: 10.1146/annurev.neuro.051508.135600

37. Namba T, Huttner WB. Neural progenitor cells and their role in the development and evolutionary expansion of the neocortex. WIREs Developmental Biology. 2017 Jan 16;6(1). doi: 10.1002/wdev.256

38. Aloisi F. Immune function of microglia. Glia. 2001;36(2):165–79. doi: 10.1002/glia.1106

39. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. Science (1979). 2011;333(6048):1456–8. doi: 10.1126/science.1202529

40. Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiol Rev. 2018;98(1):239–389. doi: 10.1152/physrev.00042.2016

41. Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiol Rev. 2018;98(1):239–389. doi: 10.1152/physrev.00042.2016

42. Burda JE, Bernstein AM, Sofroniew M V. Astrocyte roles in traumatic brain injury. Exp Neurol. 2016;275:305–15. doi: 10.1016/j.expneurol.2015.03.020

43. Hart CG, Karimi-Abdolrezaee S. Recent insights on astrocyte mechanisms in CNS homeostasis, pathology, and repair. J Neurosci Res. 2021;99(10):2427–62. doi: 10.1002/jnr.24922

44. Porras O, Ruminot I, Loasiza A, Barros L. Na1-Ca21 Cosignaling in the Stimulation of the Glucose Transporter GLUT1 in Cultured Astrocytes. Glia. 2008;56:59–68. doi: 10.1002/glia

45. Morgello S, Uson RR, Schwartz EJ, Haber RS. The human blood-brain barrier glucose transporter (GLUT1) is a glucose transporter of gray matter astrocytes. Glia. 1995;14(1):43–54. doi: 10.1002/glia.440140107

46. Ioghen O, Chițoiu L, Gherghiceanu M, Ceafalan LC, Hinescu ME. CD36 – A novel molecular target in the neurovascular unit. European Journal of Neuroscience. 2021;53(8):2500–10. doi: 10.1111/ejn.15147

47. Ebrahimi M, Yamamoto Y, Sharifi K, Kida H, Kagawa Y, Yasumoto Y, et al. Astrocyte-expressed FABP7 regulates dendritic morphology and excitatory synaptic function of cortical neurons. Glia. 2016;64(1):48–62. doi: 10.1002/glia.22902

48. Konings SC, Torres-Garcia L, Martinsson I, Gouras GK. Astrocytic and Neuronal Apolipoprotein E Isoforms Differentially Affect Neuronal Excitability. Front Neurosci. 2021;15(September):1–16. doi: 10.3389/fnins.2021.734001

49. Lanfranco MF, Sepulveda J, Kopetsky G, Rebeck GW. Expression and secretion of apoE isoforms in astrocytes and microglia during inflammation. Glia. 2021;69(6):1478–93. doi: 10.1002/glia.23974

50. Jackson RJ, Meltzer JC, Nguyen H, Commins C, Bennett RE, Hudry E, et al. APOE4 derived from astrocytes leads to blood-brain barrier impairment. Brain. 2022;145(10):3582–93. doi: 10.1093/brain/awab478

51. Mahan TE, Wang C, Bao X, Choudhury A, Ulrich JD, Holtzman DM. Selective reduction of astrocyte apoE3 and apoE4 strongly reduces Aβ accumulation and plaque-related pathology in a mouse model of amyloidosis. Mol Neurodegener. 2022;17(1):1–20. doi: 10.1186/s13024-022-00516-0

52. Koizumi S, Fujishita K, Inoue K. Regulation of cell-to-cell communication mediated by astrocytic ATP in the CNS. Purinergic Signal. 2005;1(3):211–7. doi: 10.1007/s11302-005-6321-y

53. Kim SK, Nabekura J, Koizumi S. Astrocyte-mediated synapse remodeling in the pathological brain. Glia. 2017;65(11):1719–27. doi: 10.1002/glia.23169

54. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. 2009;32(8):421–31. doi: 10.1016/j.tins.2009.05.001

55. Parkin GM, Udawela M, Gibbons A, Dean B. Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of

schizophrenia and affective disorders. World J Psychiatry. 2018;8(2):51–63. doi: 10.5498/wjp.v8.i2.51

56. Mölders A, Koch A, Menke R, Klöcker N. Heterogeneity of the astrocytic AMPA-receptor transcriptome. Glia. 2018;66(12):2604–16. doi: 10.1002/glia.23514

57. Obara-Michlewska M. The contribution of metabolic disturbances astrocytes to obesity-associated metabolic disturbances. 2022;36(5):299–311.

58. Yu G, Cao F, Hou T, Cheng Y, Jia B, Yu L, et al. Astrocyte reactivation in medial prefrontal cortex contributes to obesity - promoted depressive - like behaviors. J Neuroinflammation. 2022;1–18. doi: 10.1186/s12974-022-02529-4

59. Jimenez-Blasco D, Santofimia-Castanõ P, Gonzalez A, Almeida A, Bolanõs JP. Astrocyte NMDA receptors' activity sustains neuronal survival through a Cdk5-Nrf2 pathway. Cell Death Differ. 2015;22(11):1877–89. doi: 10.1038/cdd.2015.49

60. Boddum K, Jensen TP, Magloire V, Kristiansen U, Rusakov DA, Pavlov I, et al. Astrocytic GABA transporter activity modulates excitatory neurotransmission. Nat Commun. 2016;7:1–10. doi: 10.1038/ncomms13572

61. Wang J, Li Z, Feng M, Ren K, Shen G, Zhao C, et al. Opening of Astrocytic Mitochondrial ATP-Sensitive Potassium Channels Upregulates Electrical Coupling between Hippocampal Astrocytes in Rat Brain Slices. PLoS One. 2013;8(2). doi: 10.1371/journal.pone.0056605

62. Bolaños JP. Bioenergetics and redox adaptations of astrocytes to neuronal activity. J Neurochem. 2016;139:115–25. doi: 10.1111/jnc.13486

63. Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C. Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives. Front Physiol. 2022;12(January). doi: 10.3389/fphys.2021.825816

64. Takahashi S. Neuroprotective function of high glycolytic activity in astrocytes: Common roles in stroke and neurodegenerative diseases. Int J Mol Sci. 2021;22(12). doi: 10.3390/ijms22126568

65. Erlichman JS, Hewitt A, Damon TL, Hart M, Kurascz J, Li A, et al. Inhibition of monocarboxylate transporter 2 in the retrotrapezoid nucleus in rats: A test of the astrocyte-neuron lactate-shuttle hypothesis. Journal of Neuroscience. 2008;28(19):4888–96. doi: 10.1523/JNEUROSCI.5430-07.2008

66. Iqbal Z, Liu S, Lei Z, Ramkrishnan AS, Akter M, Li Y. Astrocyte L-Lactate Signaling in the ACC Regulates Visceral Pain Aversive Memory in Rats. Cells. 2023;12(1). doi: 10.3390/cells12010026

67. Xiong Y, Sun S, Teng S, Jin M, Zhou Z. Ca2+-Dependent and Ca2+-Independent ATP Release in Astrocytes. Front Mol Neurosci. 2018;11(July):1–5. doi: 10.3389/fnmol.2018.00224

68. Coco S, Calegari F, Pravettoni E, Pozzi D, Taverna E, Rosa P, et al. Storage and Release of ATP from Astrocytes in Culture. Journal of Biological Chemistry. 2003;278(2):1354–62. doi: 10.1074/jbc.M209454200

69. Harada K, Kamiya T, Tsuboi T. Gliotransmitter Release from Astrocytes : Functional , Developmental , and Pathological Implications in the Brain. 2016;9(January):1–9. doi: 10.3389/fnins.2015.00499

70. Verkhratsky A. Glial calcium signaling in physiology and pathophysiology. Acta Pharmacol Sin. 2006;27(7):773–80. doi: 10.1111/j.1745-7254.2006.00396.x

71. Verkhratsky A, Parpura V. Recent advances in (patho)physiology of astroglia. Acta Pharmacol Sin. 2010;31(9):1044–54. doi: 10.1038/aps.2010.108

72. Verkhratsky A. Glial calcium signaling in physiology and pathophysiology. Acta Pharmacol Sin. 2006;27(7):773–80. doi: 10.1111/j.1745-7254.2006.00396.x

73. Fields RD, Stevens-graham B. New Insights into Neuron-Glia Communication. 2002;298(October):556–63.

74. Yao Y, Chen ZL, Norris EH, Strickland S. Astrocytic laminin regulates pericyte differentiation and maintains blood brain barrier integrity. Nat Commun. 2014;5:1–12. doi: 10.1038/ncomms4413

75. Yonezawa T, Hattori S, Inagaki J, Kurosaki M, Takigawa T, Hirohata S, et al. Type IV collagen induces expression of thrombospondin-1 that is mediated by integrin $\alpha 1\beta 1$ in astrocytes. Glia. 2010;58(7):755–67. doi: 10.1002/glia.20959

76. Chistyakov D V., Nikolskaya AI, Goriainov S V., Astakhova AA, Sergeeva MG. Inhibitor of hyaluronic acid synthesis 4-methylumbelliferone as an anti-inflammatory modulator of lps-mediated astrocyte responses. Int J Mol Sci. 2020;21(21):1–16. doi: 10.3390/ijms21218203

77. Yin KJ, Cirrito JR, Yan P, Hu X, Xiao Q, Pan X, et al. Matrix Metalloproteinases Expressed by Astrocytes Mediate Extracellular Amyloid-β Peptide Catabolism. The Journal of Neuroscience. 2006 Oct 25;26(43):10939–48. doi: 10.1523/JNEUROSCI.2085-06.2006

78. Kinoshita M, Nasu-Tada K, Fujishita K, Sato K, Koizumi S. Secretion of Matrix Metalloproteinase-9 from Astrocytes by Inhibition of Tonic P2Y14-Receptor-Mediated Signal(s). Cell Mol Neurobiol. 2013 Jan 8;33(1):47–58. doi: 10.1007/s10571-012-9869-4

79. Hyvärinen T, Hagman S, Ristola M, Sukki L, Veijula K, Kreutzer J, et al. Co-stimulation with IL-1β and TNF-α induces an inflammatory reactive astrocyte phenotype with neurosupportive characteristics in a human pluripotent stem cell model system. Sci Rep. 2019;9(1):1–15. doi: 10.1038/s41598-019-53414-9

80. Liu X, Nemeth DP, McKim DB, Zhu L, DiSabato DJ, Berdysz O, et al. Cell-Type-Specific Interleukin 1 Receptor 1 Signaling in the Brain Regulates Distinct Neuroimmune Activities. Immunity. 2019;50(2):317-333.e6. doi: 10.1016/j.immuni.2018.12.012

81. Norden DM, Trojanowski PJ, Walker FR, Godbout JP. Neurobiology of Aging Insensitivity of astrocytes to interleukin 10 signaling following peripheral immune challenge results in prolonged microglial activation in the aged brain. Neurobiol Aging. 2016;44:22–41. doi: 10.1016/j.neurobiolaging.2016.04.014

82. Luo X, Tai WL, Sun L, Pan Z, Xia Z, Chung SK, et al. Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain. Mol Pain. 2016;12:1–15. doi: 10.1177/1744806916636385

83. O'Leary LA, Davoli MA, Belliveau C, Tanti A, Ma JC, Farmer WT, et al. Characterization of Vimentin-Immunoreactive Astrocytes in the Human Brain. Front Neuroanat. 2020;14(July). doi: 10.3389/fnana.2020.00031

84. Reid JK, Kuipers HF. She Doesn't Even Go Here: The Role of Inflammatory Astrocytes in CNS Disorders. Front Cell Neurosci. 2021;15(September):1–12. doi: 10.3389/fncel.2021.704884

85. Zheng K, Huang H, Yang J, Qiu M. Origin, molecular specification, and stemness of astrocytes. Dev Neurobiol. 2022;82(2):149–59. doi: 10.1002/dneu.22863

86. Griffin W, Cunningham XC, Hennessy E. Astrocytes Are Primed by Chronic Neurodegeneration to Produce Exaggerated Chemokine and Cell Infiltration Responses to Acute Stimulation with the Cytokines IL-1$_{\beta}$ and TNF-$_{\alpha}$. 2015;35(22):8411–22. doi: 10.1523/JNEUROSCI.2745-14.2015

87. Lopez-Rodriguez AB, Hennessy E, Murray CL, Nazmi A, Delaney HJ, Healy D, et al. Acute systemic inflammation exacerbates neuroinflammation in Alzheimer's disease : IL-1 β drives amplified responses in primed astrocytes and neuronal network dysfunction. 2021;(March):1735–55. doi: 10.1002/alz.12341

88. Bugiani M, Plug BC, Man JHK, Breur M, Knaap MS Van Der. Heterogeneity of white matter astrocytes in the human brain. Acta Neuropathol. 2022;143(2):159–77. doi: 10.1007/s00401-021-02391-3

89. Liddelow SA, Barres BA. Reactive Astrocytes: Production, Function, and Therapeutic Potential. Immunity. 2017;46(6):957–67. doi: 10.1016/j.immuni.2017.06.006

90. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. Vol. 24, Nature Neuroscience. Nature Research; 2021. p. 312–25. doi: 10.1038/s41593-020-00783-4

91. Jones E V., Bouvier DS. Astrocyte-secreted matricellular proteins in CNS remodelling during development and disease. Neural Plast. 2014;2014. doi: 10.1155/2014/321209

92. Allnoch L, Leitzen E, Zdora I, Baumgärtner W, Hansmann F. Astrocyte depletion alters extracellular matrix composition in the demyelinating phase of Theiler's murine encephalomyelitis. PLoS One. 2022;17(6 June):1–17. doi: 10.1371/journal.pone.0270239

93. Das S, Li Z, Noori A, Hyman BT, Serrano-Pozo A. Meta-analysis of mouse transcriptomic studies supports a context-dependent astrocyte reaction in acute CNS injury versus neurodegeneration. J Neuroinflammation. 2020;17(1):1–17. doi: 10.1186/s12974-020-01898-y

94. Bellaver B, Povala G, Ferreira PCL, Ferrari-souza JP, Leffa DT, Lussier FZ, et al. Astrocyte reactivity influences amyloid-β effects on tau pathology in preclinical Alzheimer's disease. 2023;29(July). doi: 10.1038/s41591-023-02380-x

95.   Smit T, Borchelt DR, Hol EM. Reactive astrocytes as treatment targets in Alzheimer's disease — Systematic review of studies using the APPswePS1dE9 mouse model. 2021;(February):1852–81. doi: 10.1002/glia.23981

96.   Guttenplan KA, Weigel MK, Adler DI, Couthouis J, Gitler AD, Barres BA, et al. Knockout of reactive astrocyte activating factors slows disease progression in an ALS mouse model. Nat Commun. (2020):1–9. doi: 10.1038/s41467-020-17514-9

97.   Sonninen TM, Hämäläinen RH, Koskuvi M, Oksanen M, Shakirzyanova A, Wojciechowski S, et al. Metabolic alterations in Parkinson's disease astrocytes. Sci Rep. 2020; doi: 10.1038/s41598-020-71329-8

98.   Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, Sánchez-Margalet V. Role of leptin in inflammation and vice versa. Int J Mol Sci. 2020;21(16):1–24. doi: 10.3390/ijms21165887

99.   Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Archives of Medical Science. 2017;4:851–63. doi: 10.5114/aoms.2016.58928

100.   Henn RE, Noureldein MH, Elzinga SE, Kim B, Savelieff MG, Feldman EL. Neurobiology of Disease Glial-neuron crosstalk in health and disease : A focus on metabolism , obesity , and cognitive impairment. Neurobiol Dis. 2022;170(May):105766. doi: 10.1016/j.nbd.2022.105766

101.   Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. Nature Publishing Group. 2017;18(4):225–42. doi: 10.1038/nri.2017.125

102.   Simons M, Nave K armin. Oligodendrocytes: Myelination and Axonal Support. 2016;1–15.

103.   Sofroniew M V. Astrocyte Reactivity: Subtypes, States, and Functions in CNS Innate Immunity. Trends Immunol. 2020;41(9):758–70. doi: 10.1016/j.it.2020.07.004

104.   Jiwaji Z, Tiwari SS, Avilés-Reyes RX, Hooley M, Hampton D, Torvell M, et al. Reactive astrocytes acquire neuroprotective as well as deleterious signatures in response to Tau and Aß pathology. Nat Commun. 2022;13(1). doi: 10.1038/s41467-021-27702-w

105.   Jurga AM, Paleczna M, Kadluczka J, Kuter KZ. Beyond the GFAP-astrocyte protein markers in the brain. Biomolecules. 2021;11(9). doi: 10.3390/biom11091361

106.   Buckman LB, Thompson MM, Moreno HN, Ellacott KLJ. Regional astrogliosis in the mouse hypothalamus in response to obesity. Journal of Comparative Neurology. 2013;521(6):1322–33. doi: 10.1002/cne.23233

107.   Robb JL, Hammad NA, Weightman Potter PG, Chilton JK, Beall C, Ellacott KLJ. The metabolic response to inflammation in astrocytes is regulated by nuclear factor-kappa B signaling. Glia. 2020;68(11):2246–63. doi: 10.1002/glia.23835

108.   Sheng WS, Hu S, Feng A, Rock RB. Reactive oxygen species from human astrocytes induced functional impairment and oxidative damage. Neurochem Res. 2013;38(10):2148–59. doi: 10.1007/s11064-013-1123-z

109. Boisvert MM, Erikson GA, Shokhirev MN, Allen NJ. The Aging Astrocyte Transcriptome from Multiple Regions of the Mouse Brain. Cell Rep. 2018;22(1):269–85. doi: 10.1016/j.celrep.2017.12.039

110. Clarke LE, Liddelow SA, Chakraborty C, Münch AE, Heiman M, Barres BA. Normal aging induces A1-like astrocyte reactivity. Proc Natl Acad Sci U S A. 2018;115(8):E1896–905. doi: 10.1073/pnas.1800165115

111. Pan J, Ma N, Yu B, Zhang W, Wan J. Transcriptomic profiling of microglia and astrocytes throughout aging. J Neuroinflammation. 2020;17(1):1–19. doi: 10.1186/s12974-020-01774-9

112. Ahnstedt H, Roy-O'Reilly M, Spychala MS, Mobley AS, Bravo-Alegria J, Chauhan A, et al. Sex differences in adipose tissue CD8+ T cells and regulatory T cells in middle-aged mice. Front Immunol. 2018;9(APR):1–10. doi: 10.3389/fimmu.2018.00659

113. Manuel RSJ, Liang Y. Sexual dimorphism in immunometabolism and autoimmunity: Impact on personalized medicine. Autoimmun Rev. 2021;20(4):102775. doi: 10.1016/j.autrev.2021.102775

114. Gatto N, Dos Santos Souza C, Shaw AC, Bell SM, Myszczynska MA, Powers S, et al. Directly converted astrocytes retain the ageing features of the donor fibroblasts and elucidate the astrocytic contribution to human CNS health and disease. Aging Cell. 2021;20(1):1–22. doi: 10.1111/acel.13281

115. Capece D, Verzella D, Flati I, Arboretto P, Cornice J, Franzoso G. NF-κB: blending metabolism, immunity, and inflammation. Trends Immunol. 2022;43(9):757–75. doi: 10.1016/j.it.2022.07.004

116. Mauro C, Leow SC, Anso E, Rocha S, Thotakura AK, Tornatore L, et al. NF-κB controls energy homeostasis and metabolic adaptation by upregulating mitochondrial respiration. Nat Cell Biol. 2011;13(10):1272–9. doi: 10.1038/ncb2324

117. Wang X, Lin Y. Tumor necrosis factor and cancer, buddies or foes? Acta Pharmacol Sin. 2008;29(11):1275–88. doi: 10.1111/j.1745-7254.2008.00889.x

118. Verkhratsky A, Marutle A, Rodríguez-Arellano JJ, Nordberg A. Glial Asthenia and Functional Paralysis: A New Perspective on Neurodegeneration and Alzheimers Disease. Neuroscientist. 2015;21(5):552–68. doi: 10.1177/1073858414547132

119. Hildebrandt X, Ibrahim M, Peltzer N. Cell death and inflammation during obesity: "Know my methods, WAT(son)". Cell Death Differ. 2023;30(2):279–92. doi: 10.1038/s41418-022-01062-4

120. Sun Y, Koyama Y, Shimada S. Inflammation From Peripheral Organs to the Brain: How Does Systemic Inflammation Cause Neuroinflammation? Front Aging Neurosci. 2022;14(June):1–10. doi: 10.3389/fnagi.2022.903455

121. Clark IC, Gutiérrez-Vázquez C, Wheeler MA, Li Z, Rothhammer V, Linnerbauer M, et al. Barcoded viral tracing of single-cell interactions in central nervous system inflammation. Science (1979). 2021;372(6540). doi: 10.1126/science.abf1230

122. Weightman Potter PG, Vlachaki Walker JM, Robb JL, Chilton JK, Williamson R, Randall AD, et al. Basal fatty acid oxidation increases after recurrent low glucose in human

primary astrocytes. Diabetologia. 2019;62(1):187–98. doi: 10.1007/s00125-018-4744-6

123.   Preman P, Tcw J, Calafate S, Snellinx A, Alfonso-Triguero M, Corthout N, et al. Human iPSC-derived astrocytes transplanted into the mouse brain undergo morphological changes in response to amyloid-β plaques. Mol Neurodegener. 2021;16(1):1–18. doi: 10.1186/s13024-021-00487-8

124.   Qi G, Mi Y, Shi X, Gu H, Brinton RD, Yin F. ApoE4 Impairs Neuron-Astrocyte Coupling of Fatty Acid Metabolism. Cell Rep. 2021;34(1):108572. doi: 10.1016/j.celrep.2020.108572

125.   Fuente-Martin E, Garcia-Caceres C, Morselli E, Clegg DJ, Chowen JA, Finan B, et al. Estrogen, astrocytes and the neuroendocrine control of metabolism. Rev Endocr Metab Disord. 2013;14(4):331–8. doi: 10.1007/s11154-013-9263-7

126.   Tognatta R, Karl MT, Fyffe-Maricich SL, Popratiloff A, Garrison ED, Schenck JK, et al. Astrocytes Are Required for Oligodendrocyte Survival and Maintenance of Myelin Compaction and Integrity. Front Cell Neurosci. 2020;14(April):1–17. doi: 10.3389/fncel.2020.00074

127.   Kullmann S, Abbas Z, Machann J, Shah NJ, Scheffler K, Birkenfeld AL, et al. Investigating obesity-associated brain inflammation using quantitative water content mapping. J Neuroendocrinol. 2020;32(12):1–13. doi: 10.1111/jne.12907

128.   Zhang R, Liu Y, Chen Y, Li Q, Marshall C, Wu T, et al. Aquaporin 4 deletion exacerbates brain impairments in a mouse model of chronic sleep disruption. CNS Neurosci Ther. 2020;26(2):228–39. doi: 10.1111/cns.13194

129.   Lu H, Ai L, Zhang B. TNF-α induces AQP4 overexpression in astrocytes through the NF-κB pathway causing cellular edema and apoptosis. Biosci Rep. 2022;42(3):1–13. doi: 10.1042/BSR20212224

130.   Popov A, Brazhe N, Fedotova A, Tiaglik A, Bychkov M, Morozova K, et al. A high-fat diet changes astrocytic metabolism to promote synaptic plasticity and behavior. Acta Physiologica. 2022;236(1):1–14. doi: 10.1111/apha.13847

131.   Douglass JD, Dorfman MD, Fasnacht R, Shaffer LD, Thaler JP. Astrocyte IKKβ/NF-κB signaling is required for diet-induced obesity and hypothalamic inflammation. Mol Metab [Internet]. 2017;6(4):366–73. doi: 10.1016/j.molmet.2017.01.010

132.   Balland E, Cowley MA. Short-term high-fat diet increases the presence of astrocytes in the hypothalamus of C57BL6 mice without altering leptin sensitivity. J Neuroendocrinol. 2017;29(10):1–7. doi: 10.1111/jne.12504

133.   Li TC, Li CI, Liu CS, Lin CH, Yang SY, Lin CC. Obesity marker trajectories and cognitive impairment in older adults: a 10-year follow-up in Taichung community health study for elders. BMC Psychiatry. 2022;22(1):1–11. doi: 10.1186/s12888-022-04420-1

134.   Balasubramanian P, Kiss T, Tarantini S, Nyúl-Toth Á, Ahire C, Yabluchanskiy A, et al. Obesity-induced cognitive impairment in older adults: A microvascular perspective. Am J Physiol Heart Circ Physiol. 2021;320(2):H740–61. doi: 10.1152/AJPHEART.00736.2020

135. Gardener H, Caunca M, Dong C, Cheung YK, Rundek T, Elkind MSV, et al. Obesity Measures in Relation to Cognition in the Northern Manhattan Study. Journal of Alzheimer's Disease. 2020;78(4):1653–60. doi: 10.3233/JAD-201071

136. Kim EH, Koh EH, Park JY, Lee KU. Adenine Nucleotide Translocator as a Regulator of Mitochondrial Function: Implication in the Pathogenesis of Metabolic Syndrome. Korean Diabetes J. 2010;34(3):146. doi: 10.4093/kdj.2010.34.3.146

137. Nolfi-Donegan D, Braganza A, Shiva S. Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement. Redox Biol. 2020;37:101674. doi: 10.1016/j.redox.2020.101674

138. Strogulski NR, Portela L V., Polster BM, Loane DJ. Fundamental Neurochemistry Review: Microglial immunometabolism in traumatic brain injury. J Neurochem. 2023;(July):1–25. doi: 10.1111/jnc.15959

139. Youle RJ, Bliek AM Van Der, Complementation FP, Mitochondria BD, Fusion M, Proteins F. REVIEW Mitochondrial Fission, Fusion, and Stress. 2012;337(August):1062–6.

140. Audano M, Pedretti S, Ligorio S, Crestani M, Caruso D, De Fabiani E, et al. 'The Loss of Golden Touch': Mitochondria-Organelle Interactions, Metabolism, and Cancer. Cells. 2020;9(11). doi: 10.3390/cells9112519

141. Chen C, Mossman E, Malko P, McDonald D, Blain AP, Bone L, et al. Astrocytic Changes in Mitochondrial Oxidative Phosphorylation Protein Levels in Parkinson's Disease. Movement Disorders. 2022;37(2):302–14. doi: 10.1002/mds.28849

142. Ignatenko O, Malinen S, Rybas S, Vihinen H, Nikkanen J, Kononov A, et al. Mitochondrial dysfunction compromises ciliary homeostasis in astrocytes. Journal of Cell Biology. 2023;222(1). doi: 10.1083/jcb.202203019

143. Wilson CL, Natarajan V, Hayward SL, Khalimonchuk O, Kidambi S. Mitochondrial dysfunction and loss of glutamate uptake in primary astrocytes exposed to titanium dioxide nanoparticles. Nanoscale. 2015;7(44):18477–88. doi: 10.1039/c5nr03646a

144. Morales-Rosales SL, Santín-Márquez R, Posadas-Rodriguez P, Rincon-Heredia R, Montiel T, Librado-Osorio R, et al. Senescence in Primary Rat Astrocytes Induces Loss of the Mitochondrial Membrane Potential and Alters Mitochondrial Dynamics in Cortical Neurons. Front Aging Neurosci. 2021;13(December):1–13. doi: 10.3389/fnagi.2021.766306

145. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature. 2016;535(7613):551–5. doi: 10.1038/nature18928

146. Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: Recent advances. Mol Neurodegener. 2020;15(1):1–22. doi: 10.1186/s13024-020-00376-6

147. Patel MR, Weaver AM. Astrocyte-derived small extracellular vesicles promote synapse formation via fibulin-2-mediated TGF-β signaling. Cell Rep. 2021;34(10):108829. doi: 10.1016/j.celrep.2021.108829

148. Zehnder T, Petrelli F, Romanos J, De Oliveira Figueiredo EC, Lewis TL, Déglon N, et al. Mitochondrial biogenesis in developing astrocytes regulates astrocyte maturation and synapse formation. Cell Rep. 2021;35(2). doi: 10.1016/j.celrep.2021.108952

149. Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, et al. PGC-1α deficiency causes multi-system energy metabolic derangements: Muscle dysfunction, abnormal weight control and hepatic steatosis. PLoS Biol. 2005;3(4):0672–87. doi: 10.1371/journal.pbio.0030101

150. Vernier M, Giguère V. Aging, senescence and mitochondria: The pgc-1/err axis. J Mol Endocrinol. 2021;66(1):R1–14. doi: 10.1530/JME-20-0196

151. Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, et al. PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. Sci Transl Med. 2010;2(52). doi: 10.1126/scitranslmed.3001059

152. Guo X, Dason ES, Zanon-Moreno V, Jiang Q, Nahirnyj A, Chan D, et al. PGC-1α signaling coordinates susceptibility to metabolic and oxidative injury in the inner retina. American Journal of Pathology. 2014;184(4):1017–29. doi: 10.1016/j.ajpath.2013.12.012

153. Dietrich MO, Liu ZW, Horvath TL. Mitochondrial dynamics controlled by mitofusins regulate agrp neuronal activity and diet-induced obesity. Cell. 2013;155(1):188. doi: 10.1016/j.cell.2013.09.004

154. Wang J, Lin X, Zhao N, Dong G, Wu W, Huang K, et al. Effects of Mitochondrial Dynamics in the Pathophysiology of Obesity. Frontiers in Bioscience - Landmark. 2022;27(3):1–8. doi: 10.31083/j.fbl2703107

155. González-García I, Le Thuc O, Jastroch M, García-Cáceres C. Divide et impera: How mitochondrial fission in astrocytes rules obesity. Mol Metab. 2021;45(Figure 1):2020–2. doi: 10.1016/j.molmet.2020.101159

156. Dai W, Jiang L. Dysregulated Mitochondrial Dynamics and Metabolism in Obesity, Diabetes, and Cancer. Front Endocrinol (Lausanne). 2019;10(September):1–10. doi: 10.3389/fendo.2019.00570

157. Rambold AS, Kostelecky B, Elia N, Lippincott-Schwartz J. Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc Natl Acad Sci U S A. 2011;108(25):10190–5. doi: 10.1073/pnas.1107402108

158. Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 2013;17(4):491–506. doi: 10.1016/j.cmet.2013.03.002

159. Abdullah MO, Zeng RX, Margerum CL, Papadopoli D, Monnin C, Punter KB, et al. Mitochondrial hyperfusion via metabolic sensing of regulatory amino acids. Cell Rep. 2022;40(7):111198. doi: 10.1016/j.celrep.2022.111198

160. Filippi BM, Abraham MA, Silva PN, Rasti M, LaPierre MP, Bauer P V., et al. Dynamin-Related Protein 1-Dependent Mitochondrial Fission Changes in the Dorsal Vagal Complex Regulate Insulin Action. Cell Rep. 2017;18(10):2301–9. doi: 10.1016/j.celrep.2017.02.035

161.   Ronan L, Alexander-Bloch AF, Wagstyl K, Farooqi S, Brayne C, Tyler LK, et al. Obesity associated with increased brain age from midlife. Neurobiol Aging. 2016;47:63–70. doi: 10.1016/j.neurobiolaging.2016.07.010

162.   Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia. 2015 Jun 31;11(6):718–26. doi: 10.1016/j.jalz.2015.05.016

163.   Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008 Sep 30;71(14):1057–64. doi: 10.1212/01.wnl.0000306313.89165.ef

164.   Vidyanti AN, Hardhantyo M, Wiratama BS, Prodjohardjono A, Hu CJ. Obesity is less frequently associated with cognitive impairment in elderly individuals: A cross-sectional study in Yogyakarta, Indonesia. Nutrients. 2020;12(2):1–13. doi: 10.3390/nu12020367

165.   Fozzato A, New LE, Griffiths JC, Patel B, Deuchars SA, Filippi BM. Manipulating mitochondrial dynamics in the NTS prevents diet-induced deficits in brown fat morphology and glucose uptake. Life Sci. 2023;328(March):121922. doi: 10.1016/j.lfs.2023.121922

166.   Varela L, Kim JG, Fernández-Tussy P, Aryal B, Liu ZW, Fernández-Hernando C, et al. Astrocytic lipid metabolism determines susceptibility to diet-induced obesity. Sci Adv. 2021;7(50):1–13. doi: 10.1126/sciadv.abj2814

167.   Wójtowicz S, Strosznajder AK, Jeżyna M, Strosznajder JB. The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders. Neurochem Res. 2020;45(5):972–88. doi: 10.1007/s11064-020-02993-5

168.   Scirpo R, Fiorotto R, Villani A, Amenduni M, Spirli C, Strazzabosco M. Stimulation of nuclear receptor peroxisome proliferator-activated receptor-γ limits NF-κB-dependent inflammation in mouse cystic fibrosis biliary epithelium. Hepatology. 2015;62(5):1551–62. doi: 10.1002/hep.28000

169.   Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. Antioxidants. 2023;12(5). doi: 10.3390/antiox12051075

170.   Naranjo V, Contreras A, Merino B, Plaza A, Lorenzo MP, García-Cáceres C, et al. Specific Deletion of the Astrocyte Leptin Receptor Induces Changes in Hippocampus Glutamate Metabolism, Synaptic Transmission and Plasticity. Neuroscience. 2020;447:182–90. doi: 10.1016/j.neuroscience.2019.10.005

171.   González-García I, García-Cáceres C. Hypothalamic astrocytes as a specialized and responsive cell population in obesity. Int J Mol Sci. 2021;22(12). doi: 10.3390/ijms22126176

172.   Hsuchou H, He Y, Kastin AJ, Tu H, Markadakis EN, Rogers RC, et al. Obesity induces functional astrocytic leptin receptors in hypothalamus. Brain. 2009;132(4):889–902. doi: 10.1093/brain/awp029

173. Fujita Y, Yamashita T. The effects of leptin on glial cells in neurological diseases. Front Neurosci. 2019;13(JUL):1–8. doi: 10.3389/fnins.2019.00828

174. Jayaram B, Pan W, Wang Y, Hsuchou H, MacE A, Cornelissen-Guillaume GG, et al. Astrocytic leptin-receptor knockout mice show partial rescue of leptin resistance in diet-induced obesity. J Appl Physiol. 2013;114(6):734–41. doi: 10.1152/japplphysiol.01499.2012

175. Debarba LK, Vechiato FMV, Veida-Silva H, Borges BC, Jamur MC, Antunes-Rodrigues J, et al. The role of TCPTP on leptin effects on astrocyte morphology. Mol Cell Endocrinol. 2019;482(November 2018):62–9. doi: 10.1016/j.mce.2018.12.010

176. Santos CL, Bobermin LD, Souza DO, Quincozes-Santos A. Leptin stimulates the release of pro-inflammatory cytokines in hypothalamic astrocyte cultures from adult and aged rats. Metab Brain Dis. 2018;33(6):2059–63. doi: 10.1007/s11011-018-0311-6

177. Lutomska LM, Miok V, Krahmer N, González García I, Gruber T, Le Thuc O, et al. Diet triggers specific responses of hypothalamic astrocytes in time and region dependent manner. Glia. 2022;70(11):2062–78. doi: 10.1002/glia.24237

178. Herrera Moro Chao D, Kirchner MK, Pham C, Foppen E, Denis RGP, Castel J, et al. Hypothalamic astrocytes control systemic glucose metabolism and energy balance. Cell Metab. 2022;34(10):1532-1547.e6. doi: 10.1016/j.cmet.2022.09.002

179. Douglass JD, Dorfman MD, Thaler JP. Glia: silent partners in energy homeostasis and obesity pathogenesis. Diabetologia [Internet]. 2017;60(2):226–36. doi: 10.1007/s00125-016-4181-3

180. Ladyman SR, Grattan DR. JAK-STAT and feeding. JAKSTAT. 2013;2(2):e23675. doi: 10.4161/jkst.23675

181. Mullen M, Gonzalez-Perez RR. Leptin-induced JAK/STAT signaling and cancer growth. Vaccines (Basel). 2016;4(3). doi: 10.3390/vaccines4030026

182. Gurzov EN, Stanley WJ, Pappas EG, Thomas HE, Gough DJ. The JAK/STAT pathway in obesity and diabetes. FEBS Journal. 2016;283:3002–15. doi: 10.1111/febs.13709

183. Liu H, Du T, Li C, Yang G. STAT3 phosphorylation in central leptin resistance. Nutr Metab (Lond). 2021;18(1):1–13. doi: 10.1186/s12986-021-00569-w

184. Flores-Cordero JA, Pérez-Pérez A, Jiménez-Cortegana C, Alba G, Flores-Barragán A, Sánchez-Margalet V. Obesity as a Risk Factor for Dementia and Alzheimer's Disease: The Role of Leptin. Int J Mol Sci. 2022;23(9). doi: 10.3390/ijms23095202

185. Pratap AA, Holsinger RMD. Altered brain leptin and leptin receptor expression in the 5xfad mouse model of alzheimer's disease. Pharmaceuticals. 2020;13(11):1–15. doi: 10.3390/ph13110401

186. Platt TL, Beckett TL, Kohler K, Niedowicz DM, Murphy MP. Obesity, diabetes, and leptin resistance promote tau pathology in a mouse model of disease. Neuroscience. 2016;315:162–74. doi: 10.1016/j.neuroscience.2015.12.011

187. García-Cáceres C, Balland E, Prevot V, Luquet S, Woods SC, Koch M, et al. Role of astrocytes, microglia, and tanycytes in brain control of systemic metabolism. Nat Neurosci. 2019;22(1):7–14. doi: 10.1038/s41593-018-0286-y

188. Fernandez AM, Martinez-Rachadel L, Navarrete M, Pose-Utrill J, Davila JC, Pignatelli J, et al. Insulin regulates neurovascular coupling through astrocytes. Proc Natl Acad Sci U S A. 2022;119(29):1–12. doi: 10.1073/pnas.2204527119

189. Chen W, Huang Q, Lazdon E, Gomes A, Wong M, Stephens E, et al. Loss of insulin signaling in astrocytes exacerbates Alzheimer-like phenotypes in a 5xFAD mouse model. Proceedings of the National Academy of Sciences. 2017;120:2017. doi: 10.1073/pnas.2220684120

190. Komleva Y, Chernykh A, Lopatina O, Gorina Y, Lokteva I, Salmina A, et al. Inflamm-Aging and Brain Insulin Resistance: New Insights and Role of Life-style Strategies on Cognitive and Social Determinants in Aging and Neurodegeneration. Front Neurosci. 2021;14(January):1–17. doi: 10.3389/fnins.2020.618395

191. Thillainadesan J, Scott IA, Le Couteur DG. Frailty, a multisystem ageing syndrome. Age Ageing. 2020;49(5):758–63. doi: 10.1093/ageing/afaa112

192. Howlett SE, Rutenberg AD, Rockwood K. The degree of frailty as a translational measure of health in aging. Nat Aging. 2021;1(8):651–65. doi: 10.1038/s43587-021-00099-3

193. Xue QL. The Frailty Syndrome: Definition and Natural History. Clin Geriatr Med. 2011;27(1):1–15. doi: 10.1016/j.cger.2010.08.009

194. Fried LP, Cohen AA, Xue QL, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nat Aging. 2021;1(1):36–46. doi: 10.1038/s43587-020-00017-z

195. Kao TW, Peng TC, Chen WL, Chi YC, Chen CL, Yang WS. Higher serum leptin levels are associated with a reduced risk of sarcopenia but a higher risk of dynapenia among older adults. J Inflamm Res. 2021;14:5817–25. doi: 10.2147/JIR.S335694

196. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease: Lessons from gerontology. Chron Respir Dis. 2017;14(1):85–99. doi: 10.1177/1479972316679664

197. Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW. Nutrition, inflammation, and leptin levels in aging and frailty. J Am Geriatr Soc. 2008;56(2):279–84. doi: 10.1111/j.1532-5415.2007.01548.x

198. Shibasaki K, Yamada S, Akishita M, Ogawa S. Plasma leptin concentration and sympathetic nervous activity in older adults with physical dysfunction. J Endocr Soc. 2018;2(9):1040–9. doi: 10.1210/JS.2018-00104

199. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients. 2019;11(11):1–11. doi: 10.3390/nu11112704

200. Kalyani RR, Varadhan R, Weiss CO. Frailty Status and Altered Dynamics of Circulating Energy. J Nutr Health Aging. 2012;16(8):679–86.

201. Heinze-Milne SD, Banga S, Howlett SE. Frailty and cytokines in preclinical models: Comparisons with humans. Mech Ageing Dev. 2022;206(April):111706. doi: 10.1016/j.mad.2022.111706

202. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8. doi: 10.1016/j.arr.2016.08.006

203. Nascimento CMC, Zazzetta MS, Gomes GAO, Orlandi FS, Gramani-Say K, Vasilceac FA, et al. Higher levels of tumor necrosis factor β are associated with frailty in socially vulnerable community-dwelling older adults. BMC Geriatr. 2018;18(1):1–9. doi: 10.1186/s12877-018-0961-6

204. Fedarko NS. The Biology of Aging and Frailty. Clin Geriatr Med. 2011;27(1):27–37. doi: 10.1016/j.cger.2010.08.006

205. Labandeira-Garcia JL, Costa-Besada MA, Labandeira CM, Villar-Cheda B, Rodríguez-Perez AI. Insulin-like growth factor-1 and neuroinflammation. Front Aging Neurosci. 2017;9(NOV):1–9. doi: 10.3389/fnagi.2017.00365

206. Pinto-Benito D, Paradela-Leal C, Ganchala D, de Castro-Molina P, Arevalo MA. IGF-1 regulates astrocytic phagocytosis and inflammation through the p110α isoform of PI3K in a sex-specific manner. Glia. 2022;70(6):1153–69. doi: 10.1002/glia.24163

207. Goulet EDB, Hassaine A, Dionne IJ, Gaudreau P, Khalil A, Fulop T, et al. Frailty in the elderly is associated with insulin resistance of glucose metabolism in the postabsorptive state only in the presence of increased abdominal fat. Exp Gerontol. 2009;44(11):740–4. doi: 10.1016/j.exger.2009.08.008

208. Ratcliffe LE, Vázquez Villaseñor I, Jennings L, Heath PR, Mortiboys H, Schwartzentruber A, et al. Loss of IGF1R in Human Astrocytes Alters Complex I Activity and Support for Neurons. Neuroscience. 2018;390:46–59. doi: 10.1016/j.neuroscience.2018.07.029

209. Bako HY, Ibrahim MA, Isah MS, Ibrahim S. Inhibition of JAK-STAT and NF-κB signalling systems could be a novel therapeutic target against insulin resistance and type 2 diabetes. Life Sci. 2019;239(November):117045. doi: 10.1016/j.lfs.2019.117045

210. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019;15(10):565–81. doi: 10.1038/s41582-019-0244-7

211. Razay G, Vreugdenhil A, Wilcock G. Obesity, abdominal obesity and Alzheimer disease. Dement Geriatr Cogn Disord. 2006;22(2):173–6. doi: 10.1159/000094586

212. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-Analysis : Overweight , Obesity , and Parkinson ' s Disease. 2014;2014.

213. Meo SA, Altuwaym AA, Alfallaj RM, Alduraibi KA, Alhamoudi AM, Alghamdi SM, et al. Effect of obesity on cognitive function among school adolescents: A cross-sectional study. Obes Facts. 2019;12(2):150–6. doi: 10.1159/000499386

214. Smith L, Toussaint L, Micoli A, Lynch B. Obesity, putative biological mediators, and cognitive function in a national sample of children and adolescents. Prev Med (Baltim). 2021;150(June):106659. doi: 10.1016/j.ypmed.2021.106659

215. Cheke LG, Simons JS, Clayton NS. Higher body mass index is associated with episodic memory deficits in young adults. Quarterly Journal of Experimental Psychology. 2016;69(11):2305–16. doi: 10.1080/17470218.2015.1099163

216. Brunstrom JM, Burn JF, Sell NR, Collingwood JM, Rogers PJ, Wilkinson LL, et al. Episodic Memory and Appetite Regulation in Humans. PLoS One. 2012;7(12). doi: 10.1371/journal.pone.0050707

217. Robinson E, Aveyard P, Daley A, Jolly K, Lewis A, Lycett D, et al. Eating attentively: A systematic review and meta-analysis of the effect of food intake memory and awareness on eating. American Journal of Clinical Nutrition. 2013;97(4):728–42. doi: 10.3945/ajcn.112.045245

218. Spitznagel MB, Alosco M, Galioto R, Strain G, Devlin M, Sysko R, et al. The role of cognitive function in postoperative weight loss outcomes: 36-Month follow-up. Obes Surg. 2014;24(7):1078–84. doi: 10.1007/s11695-014-1205-2

219. Spitznagel MB, Garcia S, Miller LA, Strain G, Devlin M, Wing R, et al. Cognitive function predicts weight loss after bariatric surgery. Surgery for Obesity and Related Diseases. 2013;9(3):453–9. doi: 10.1016/j.soard.2011.10.008

220. Siervo M, Arnold R, Wells JCK, Tagliabue A, Colantuoni A, Albanese E, et al. Intentional weight loss in overweight and obese individuals and cognitive function: A systematic review and meta-analysis. Obesity Reviews. 2011;12(11):968–83. doi: 10.1111/j.1467-789X.2011.00903.x

221. Morys F, Potvin O, Zeighami Y, Vogel J, Lamontagne-Caron R, Duchesne S, et al. Obesity-Associated Neurodegeneration Pattern Mimics Alzheimer's Disease in an Observational Cohort Study. Journal of Alzheimer's Disease. 2023;91(3):1059–71. doi: 10.3233/JAD-220535

222. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. Neurology. 2011;76(18):1568–74. doi: 10.1212/WNL.0b013e3182190d09

223. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, et al. Midlife and late-life obesity and the risk of dementia: Cardiovascular health study. Arch Neurol. 2009;66(3):336–42. doi: 10.1001/archneurol.2008.582

224. Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: A systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016;45(1):14–21. doi: 10.1093/ageing/afv151

225. Morys F, Dadar M, Dagher A. Association between midlife obesity and its metabolic consequences, cerebrovascular disease, and cognitive decline. Journal of Clinical Endocrinology and Metabolism. 2021;106(10):E4260–74. doi: 10.1210/clinem/dgab135

226. Picone P, Di Carlo M, Nuzzo D. Obesity and Alzheimer's disease: Molecular bases. European Journal of Neuroscience. 2020;52(8):3944–50. doi: 10.1111/ejn.14758

227. Nuzzo D, Picone P, Baldassano S, Caruana L, Messina E, Marino Gammazza A, et al. Send Orders for Reprints to reprints@benthamscience.ae Insulin Resistance as

Common Molecular Denominator Linking Obesity to Alzheimer's Disease. Curr Alzheimer Res. 2015;12:723–35.

228.   Nuzzo D, Baldassano S, Amato A, Picone P, Galizzi G, Caldara GF, et al. Glucagon-like peptide-2 reduces the obesity-associated inflammation in the brain. Neurobiol Dis. 2019;121(October 2018):296–304. doi: 10.1016/j.nbd.2018.10.012

229.   Nuzzo D, Galizzi G, Amato A, Terzo S, Picone P, Cristaldi L, et al. Regular intake of pistachio mitigates the deleterious effects of a high fat-diet in the brain of obese mice. Antioxidants. 2020;9(4):1–16. doi: 10.3390/antiox9040317

230.   Guillemot-Legris O, Muccioli GG. Obesity-Induced Neuroinflammation: Beyond the Hypothalamus. Trends Neurosci. 2017;40(4):237–53. doi: 10.1016/j.tins.2017.02.005

231.   Baufeld C, Osterloh A, Prokop S, Miller KR, Heppner FL. High-fat diet-induced brain region-specific phenotypic spectrum of CNS resident microglia. Acta Neuropathol. 2016;132(3):361–75. doi: 10.1007/s00401-016-1595-4

232.   Hubbard JA, Szu JI, Binder DK. The role of aquaporin-4 in synaptic plasticity, memory and disease. Brain Res Bull. 2018;136:118–29. doi: 10.1016/j.brainresbull.2017.02.011

233.   Tamtaji OR, Behnam M, Pourattar MA, Jafarpour H, Asemi Z. Aquaporin 4: A key player in Parkinson's disease. J Cell Physiol. 2019;234(12):21471–8. doi: 10.1002/jcp.28871

234.   Arighi A, Arcaro M, Fumagalli GG, Carandini T, Pietroboni AM, Sacchi L, et al. Aquaporin-4 cerebrospinal fluid levels are higher in neurodegenerative dementia: looking at glymphatic system dysregulation. Alzheimers Res Ther. 2022;14(1):1–10. doi: 10.1186/s13195-022-01077-6

235.   Kracht M, Müller-Ladner U, Schmitz ML. Mutual regulation of metabolic processes and proinflammatory NF-κB signaling. Journal of Allergy and Clinical Immunology. 2020;146(4):694–705. doi: 10.1016/j.jaci.2020.07.027

236.   Gruber T, Pan C, Contreras RE, Wiedemann T, Morgan DA, Skowronski AA, et al. Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. Cell Metab. 2021;33(6):1155-1170.e10. doi: 10.1016/j.cmet.2021.04.007

237.   Prakash R, Johnson M, Fagan SC, Ergul A. Cerebral Neovascularization and Remodeling Patterns in Two Different Models of Type 2 Diabetes. PLoS One. 2013;8(2). doi: 10.1371/journal.pone.0056264

238.   Yi CX, Gericke M, Krüger M, Alkemade A, Kabra DG, Hanske S, et al. High calorie diet triggers hypothalamic angiopathy. Mol Metab. 2012;1(1–2):95–100. doi: 10.1016/j.molmet.2012.08.004

239.   de Paula GC, Brunetta HS, Engel DF, Gaspar JM, Velloso LA, Engblom D, et al. Hippocampal Function Is Impaired by a Short-Term High-Fat Diet in Mice: Increased Blood–Brain Barrier Permeability and Neuroinflammation as Triggering Events. Front Neurosci. 2021;15(November):1–12. doi: 10.3389/fnins.2021.734158

240. Buckman LB, Thompson MM, Lippert RN, Blackwell TS, Yull FE, Ellacott KLJ. Evidence for a novel functional role of astrocytes in the acute homeostatic response to high-fat diet intake in mice. Mol Metab. 2015;4(1):58–63. doi: 10.1016/j.molmet.2014.10.001

241. Mateo I, Llorca J, Infante J, Rodríguez-Rodríguez E, Fernández-Viadero C, Peña N, et al. Low serum VEGF levels are associated with Alzheimer's disease. Acta Neurol Scand. 2007;116(1):56–8. doi: 10.1111/j.1600-0404.2006.00775.x

242. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc Natl Acad Sci U S A. 2002;99(18):11946–50. doi: 10.1073/pnas.182296499

243. Barna BP, Estes ML, Jacobs BS, Hudson S, Ransohoff RM. Human astrocytes proliferate in response to tumor necrosis factor alpha. J Neuroimmunol. 1990;30(2–3):239–43. doi: 10.1016/0165-5728(90)90108-Y

244. Sawada M, Suzumura A, Marunouchi T. TNFα induces IL-6 production by astrocytes but not by microglia. Brain Res. 1992;583(1–2):296–9. doi: 10.1016/S0006-8993(10)80037-X

245. Bezzi P, Domercq M, Brambilla L, Galli R, Schols D, De Clercq E, et al. CXCR4-activated astrocyte glutamate release via TNFa: Amplification by microglia triggers neurotoxicity. Nat Neurosci. 2001;4(7):702–10. doi: 10.1038/89490

246. van Neerven S, Nemes A, Imholz P, Regen T, Denecke B, Johann S, et al. Inflammatory cytokine release of astrocytes in vitro is reduced by all-trans retinoic acid. J Neuroimmunol. 2010;229(1–2):169–79. doi: 10.1016/j.jneuroim.2010.08.005

247. Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T. Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents. Neuroscience. 2002;113(3):607–15. doi: 10.1016/S0306-4522(02)00162-8

248. Oomura Y, Hori N, Shiraishi T, Fukunaga K, Takeda H, Tsuji M, et al. Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats. Peptides (NY). 2006;27(11):2738–49. doi: 10.1016/j.peptides.2006.07.001

249. Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, et al. Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity. 2010;18(3):463–9. doi: 10.1038/oby.2009.273

250. McNay EC, Ong CT, McCrimmon RJ, Cresswell J, Bogan JS, Sherwin RS. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiol Learn Mem. 2010;93(4):546–53. doi: 10.1016/j.nlm.2010.02.002

251. Liu Z, Patil IY, Jiang T, Sancheti H, Walsh JP, Stiles BL, et al. High-fat diet induces hepatic insulin resistance and impairment of synaptic plasticity. PLoS One. 2015;10(5):1–16. doi: 10.1371/journal.pone.0128274

252. Petrov D, Pedrós I, Artiach G, Sureda FX, Barroso E, Pallàs M, et al. High-fat diet-induced deregulation of hippocampal insulin signaling and mitochondrial homeostasis deficiences contribute to Alzheimer disease pathology in rodents. Biochim Biophys Acta Mol Basis Dis. 2015;1852(9):1687–99. doi: 10.1016/j.bbadis.2015.05.004

253. García-Cáceres C, Quarta C, Varela L, Gao Y, Gruber T, Legutko B, et al. Astrocytic Insulin Signaling Couples Brain Glucose Uptake with Nutrient Availability. Cell. 2016;166(4):867–80. doi: 10.1016/j.cell.2016.07.028

254. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. Physiol Rev. 2016;96(4):1169–209. doi: 10.1152/physrev.00032.2015

255. Hallschmid M. Intranasal Insulin for Alzheimer's Disease. CNS Drugs. 2021;35(1):21–37. doi: 10.1007/s40263-020-00781-x

256. Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. A C. elegans mutant that lives twice as long as wild type. Nature. 1993 Dec;366(6454):461–4. doi: 10.1038/366461a0

257. Augustin H, McGourty K, Allen MJ, Madem SK, Adcott J, Kerr F, et al. Reduced insulin signaling maintains electrical transmission in a neural circuit in aging flies. PLoS Biol. 2017 Sep 13;15(9):e2001655. doi: 10.1371/journal.pbio.2001655

258. El-Ami T, Moll L, Carvalhal Marques F, Volovik Y, Reuveni H, Cohen E. A novel inhibitor of the insulin/IGF signaling pathway protects from age-onset, neurodegeneration-linked proteotoxicity. Aging Cell. 2014 Feb 22;13(1):165–74. doi: 10.1111/acel.12171

259. Freude S, Hettich MM, Schumann C, Stöhr O, Koch L, Köhler C, et al. Neuronal IGF-1 resistance reduces Aβ accumulation and protects against premature death in a model of Alzheimer's disease. The FASEB Journal. 2009 Oct;23(10):3315–24. doi: 10.1096/fj.09-132043

260. Cohen E, Paulsson JF, Blinder P, Burstyn-Cohen T, Du D, Estepa G, et al. Reduced IGF-1 Signaling Delays Age-Associated Proteotoxicity in Mice. Cell. 2009 Dec;139(6):1157–69. doi: 10.1016/j.cell.2009.11.014

261. Gontier G, George C, Chaker Z, Holzenberger M, Aïd S. Blocking IGF Signaling in Adult Neurons Alleviates Alzheimer's Disease Pathology through Amyloid-β Clearance. The Journal of Neuroscience. 2015 Aug 19;35(33):11500–13. doi: 10.1523/JNEUROSCI.0343-15.2015

262. Killick R, Scales G, Leroy K, Causevic M, Hooper C, Irvine EE, et al. Deletion of Irs2 reduces amyloid deposition and rescues behavioural deficits in APP transgenic mice. Biochem Biophys Res Commun. 2009 Aug;386(1):257–62. doi: 10.1016/j.bbrc.2009.06.032

263. LaMoia TE, Shulman GI. Cellular and Molecular Mechanisms of Metformin Action. Endocr Rev. 2021 Jan 28;42(1):77–96. doi: 10.1210/endrev/bnaa023

264. Pedersen O, Nielsen OH, Bak J, Richelsen B, Beck-Nielsen H, Sørensen NS. The Effects of Metformin on Adipocyte Insulin Action and Metabolic Control in Obese Subjects with Type 2 Diabetes. Diabetic Medicine. 1989 Apr 30;6(3):249–56. doi: 10.1111/j.1464-5491.1989.tb01156.x

265. Aroda VR, Ratner RE. Metformin and Type 2 Diabetes Prevention. Diabetes Spectrum. 2018 Nov 1;31(4):336–42. doi: 10.2337/ds18-0020

266. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 2020 Oct;Volume 13:3611–6. doi: 10.2147/DMSO.S275898

267. Kar S, Chabot J -G., Quirion R. Quantitative autoradiographic localization of [125 I]insulin-like growth factor I, [125 I]insulin-like growth factor II, and [125 I]insulin receptor binding sites in developing and adult rat brain. Journal of Comparative Neurology. 1993 Jul 15;333(3):375–97. doi: 10.1002/cne.903330306

268. D'Ercole AJ. INSULIN-LIKE GROWTH FACTORS AND THEIR RECEPTORS IN GROWTH. Endocrinol Metab Clin North Am. 1996 Sep;25(3):573–90. doi: 10.1016/S0889-8529(05)70341-8

269. Gazit N, Vertkin I, Shapira I, Helm M, Slomowitz E, Sheiba M, et al. IGF-1 Receptor Differentially Regulates Spontaneous and Evoked Transmission via Mitochondria at Hippocampal Synapses. Neuron. 2016 Feb;89(3):583–97. doi: 10.1016/j.neuron.2015.12.034

270. Balaji V, Pokrzywa W, Hoppe T. Ubiquitylation Pathways In Insulin Signaling and Organismal Homeostasis. BioEssays. 2018 May 3;40(5). doi: 10.1002/bies.201700223

271. Lin X, Smagghe G. Roles of the insulin signaling pathway in insect development and organ growth. Peptides (NY). 2019 Dec;122:169923. doi: 10.1016/j.peptides.2018.02.001

272. Géminard C, Arquier N, Layalle S, Bourouis M, Slaidina M, Delanoue R, et al. Control of Metabolism and Growth Through Insulin-Like Peptides in *Drosophila*. Diabetes. 2006 Dec 1;55(Supplement_2):S5–8. doi: 10.2337/db06-S001

273. Cohen E, Dillin A. The insulin paradox: aging, proteotoxicity and neurodegeneration. Nat Rev Neurosci. 2008 Oct 4;9(10):759–67. doi: 10.1038/nrn2474

274. McGuire MJ, Ishii M. Leptin Dysfunction and Alzheimer's Disease: Evidence from Cellular, Animal, and Human Studies. Cell Mol Neurobiol. 2016;36(2):203–17. doi: 10.1007/s10571-015-0282-7

275. Kim JG, Suyama S, Koch M, Jin S, Argente-Arizon P, Argente J, et al. Leptin signaling in astrocytes regulates hypothalamic neuronal circuits and feeding. Nat Neurosci. 2014;17(7):908–10. doi: 10.1038/nn.3725

276. Holden KF, Lindquist K, Tylavsky FA, Rosano C, Harris TB, Yaffe K. Serum leptin level and cognition in the elderly: Findings from the Health ABC Study. Neurobiol Aging. 2009;30(9):1483–9. doi: 10.1016/j.neurobiolaging.2007.11.024

277. Maioli S, Lodeiro M, Merino-Serrais P, Falahati F, Khan W, Puerta E, et al. Alterations in brain leptin signalling in spite of unchanged CSF leptin levels in Alzheimer's disease. Aging Cell. 2015;14(1):122–9. doi: 10.1111/acel.12281

278. Volkow ND, Wang GJ, Telang F, Fowler JS, Goldstein RZ, Alia-Klein N, et al. Inverse association between BMI and prefrontal metabolic activity in healthy adults. Obesity. 2009;17(1):60–5. doi: 10.1038/oby.2008.469

279. Képes Z, Aranyi C, Forgács A, Nagy F, Kukuts K, Hascsi Z, et al. Glucose-level dependent brain hypometabolism in type 2 diabetes mellitus and obesity. Eur J Hybrid Imaging. 2021;5(1). doi: 10.1186/s41824-021-00097-z