Title: **Lipid metabolism in astrocytic structure and function**

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Abstract

Astrocytes are the most abundant glial cell in the central nervous system and are involved in multiple processes including metabolic homeostasis, blood brain barrier regulation and neuronal crosstalk. Astrocytes are the main storage point of glycogen in the brain and it is well established that astrocyte uptake of glutamate and release of lactate prevents neuronal excitability and supports neuronal metabolic function. However, the role of lipid metabolism in astrocytes in relation to neuronal support has been until recently, unclear. Lipids play a fundamental role in astrocyte function, including energy generation, membrane fluidity and cell to cell signaling. There is now emerging evidence that astrocyte storage of lipids in droplets has a crucial physiological and protective role in the central nervous system. This pathway links β-oxidation in astrocytes to inflammation, signalling, oxidative stress and mitochondrial energy generation in neurons. Disruption in lipid metabolism, structure and signalling in astrocytes can lead to pathogenic mechanisms associated with a range of neurological disorders.

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Abbreviations: Alzheimer's disease; 2-arachidonoylglycerol (2-AG); amyotrophic lateral sclerosis (ALS); blood brain barrier (BBB); cannabidiol (CBD); cannabinoid receptor (CBR); CC-Chemokine Ligand (CCCL); central nervous system (CNS); CXC-Chemokine Ligand (CXCL); diacylglycerol (DAG); diacylglycerol kinase (DGK); docosahexaenoic acid (DHA); endocannabinoid (ECB); endoplasmic reticulum (ER); fatty acid binding protein (FABP); fatty acid oxidation (FAO); glucagon-like peptide-1 (Glp 1); glutamate transporter 1 (GLT1); glutamate-aspartate transporter (GLAST); glucose transporter 1 (GLUT1); Haem oxygenase 1 (HO1) high fat diet (HFD); Interleukin-1β (IL-1β); Interleukin-10 (IL-10); Lactate Dehydrogenase (LDH); Lipid droplet(s) (LD(s)); Lipoprotein lipase (LPL); long term potentiation (LTP); lysophosphatidic acid (LPA); nuclear factor erythroid 2–related factor 2 (Nrf2); oleoylethanolamide (OEA); Parkinson's disease (PD); phosphatidic acid (PA); phosphatidylethanolamine binding protein (PEBP1); phospholipase D (PLD); polyunsaturated fatty acids (PUFA's); proliferator-activated receptor (PPAR)-α; monocarboxylate transporter 1 (MCT1); protein kinase A (PKA); N-methyl-D-aspartate (NMDA); (seladin-1)3β-Hydroxysteroid-Δ24 reductase (DHCR24);spike timing-dependent long term depression (t-LTD); Sterol

regulatory element binding protein 2 (SREBP2); tetrahydrocannabinol (THC); Toll Like Receptor 4 (TLR4); transforming growth factor β1 (TGF-β1); Tumour Necrosis Factor-α (TNF-α);

1. Introduction

The brain is made up of a network of neurons, which are supported by various types of glial cells, with astrocytes being the most abundant [1, 2]. Astrocytes are involved in various crucial functions within the central nervous system (CNS), not least neuronal support. These roles are mostly beyond the scope of this review article but have been summarised extensively in recent articles [2-4]**.** An area of research that has emerged in recent years is the importance of lipid metabolism, storage and transport in both astrocytes and neurons [5]. Recent evidence suggests that disruption in neuron-astrocyte lipid crosstalk contributes to neurological disease pathology [6-8]. Therefore, the aim of this article is to discuss the role of lipids within astrocyte structure and function under physiological conditions, and how disruption to astrocyte lipid homeostasis can contribute to neurological disorders. To set the scene, this article will initially cover a brief introduction into astrocyte function in relation to metabolism, inflammation and neuronal support. Subsequently, astrocyte lipids will be introduced and discussed in the context of new insights into astrocyte membrane structure and membrane transport. Concomitantly, the role of astrocytic lipid mobilisation, will be discussed in the context of metabolic function, the emerging role of lipid droplet formation in astrocyte neuronal cross-talk and new insights into the role of lipids in CNS signalling pathways. Finally, the article will discuss the role of astrocyte lipids in relation to neurodegenerative diseases, highlighting potential therapeutic pathways and new avenues of research.

1.1. Astrocyte support in the CNS

Astrocytes are involved in numerous functions within the brain, including regulation of blood brain barrier (BBB) integrity, maintenance of extracellular ion and neurotransmitter homeostasis,

and neuronal support [2-4]. Astrocytes support neurons in a multitude of ways, including neuronal growth and development during childhood [9] and neuronal maintenance throughout adulthood [10]. Communication between astrocytes and neurons is an important and tightly regulated process, thus making it essential for proper brain function [11]. Astrocyte membranes are enriched in glutamate transporters including glutamate transporter 1 (GLT1) and glutamate-aspartate transporter (GLAST), which allow clearance of glutamate from the synapse of neurons after neurotransmission, preventing glutamate mediated excitotoxicity [12]. This communication is also crucial for maintenance of the health and normal function of the CNS, as well as providing both metabolic and trophic support [13].

1.2. Astrocyte metabolism

Evidence suggests that neurotransmission uses the majority of energy in the brain [14] but neurons have very limited energy stores so they have to source their energy substrates such as glucose externally. However, there are tightly regulated mechanisms that ensure adequate delivery of the energy substrates in relation to the amount of neuronal activity occurring at any point [15]. Glucose is taken up by astrocyte projections through glucose transporter 1 (GLUT1) from peripheral blood circulation, concomitantly activating the glycolytic pathway [16]. For an excellent overview of glucose metabolism in the CNS see [17]. As astrocytes are predominantly glycolytic in nature [18, 19], glucose is oxidised to pyruvate and then dehydrogenated to lactate. If pyruvate is not dehydrogenated to lactate or taken up by the mitochondria and converted to acetyl-coA, gluconeogenesis can occur with excess carbon stored as glycogen for times of bioenergetic stress, however, this process is tightly regulated. Using emerging fluorophore sensor technology, a recent study suggested that mitochondria in cultured mouse astrocytes can maintain lower levels of pyruvate compared to the cytosol [20].

As pyruvate flux into the mitochondria is regulated by the mitochondrial pyruvate carrier (MPC), the authors suggest that this is an essential regulatory control point between basal respiration

and gluconeogenesis in astrocytes. Therefore, this data suggests that modulation of pathways such as gluconeogenesis may have therapeutic potential in neurological diseases where there is a significant metabolic component such as Alzheimer's disease (AD, see Zulfiqar *et al* for a recent review see [21]). For example, astrocytes expressing the E4 allele of Apo-lipoprotein E (*APOE*), a genetic risk factor for AD, were shown to have increased glucose flux via the pentose phosphate pathway (PPP). This led to a concomitant increase in gluconeogenesis as well as phospholipid and nucleotide biosynthesis compared to E3 astrocytes [22]. Moreover, an increase in gluconeogenesis was observed when the neurosteroid tibolone was used to reduce L-glutamate-mediated neurotoxicity in astrocytes [23]. Tibolone has previously been used to reduce inflammation in neurons, however emerging mechanistic analysis in murine cortical astrocytes subject to brain injury has shown that the drug also reduces reactive astrocyte levels, indicating an anti-inflammatory role in glia [24].

1.3 Inflammation

Astrocytes play an important role in CNS inflammation and undergo a range of functional and structural adaptations termed astrogliosis in response to inflammatory conditions induced by metabolic stress, infection or injury for an in depth review see [25].

Astrogliosis can exert either protective or harmful effects depending on the extent of gliosis and the specific signalling pathways activated, with evidence suggesting both inflammatory and anti-inflammatory pathways can be activated. Astrocytes have been shown to stimulate the release of, for example, the anti-inflammatory cytokine TGF-β, in response to IL-10, which attenuates inflammation in microglia [26]. Conversely astrocytes have been shown to release the pro-inflammatory cytokines Tumour Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1-β), as well as releasing CC-chemokine ligands (CCCL) and CXC-chemokine Ligands (CXCL). Certain CCCLs and CXCLs, along with TNF-α, are responsible for recruiting a diverse range of leukocytes by inducing and activating their adhesion molecules [27]. IL-1-β stimulates

astrocytes to release vascular endothelial growth factor, which increases the ability for leukocytes to cross the BBB and enter the CNS parenchyma [28].

There is a bi-directional relationship between inflammation and metabolic status not only in astrocytes but in the CNS as a whole, which is an emerging area of therapeutic research in neurological diseases [29-31]. Preventing astrocyte inflammation through nuclear factor-kappa B (NF-κB) inhibition in mice astrocytes for example, has been shown to be beneficial by; reducing glial scarring in spinal cord injury; increasing glucose tolerance and promoting energy expenditure; and increasing glucose uptake and glycolytic capacity. Moreover astrocytic glycolytic inhibition by 2-deoxyglucose has recently been shown to significantly reduce LPS-induced cytokine release and NF-κB phosphorylation [32-34]. There is also emerging evidence of a link between astrocyte lipid signalling and the metabolic inflammatory response which will be discussed in section 2.

1.4 Astrocyte metabolic support of neurons

Astrocytes have been proposed to support neurons metabolically via the release of lactate [35], however this is still a controversial area. In order for this theory to remain true, it was proposed that neuronal glucose metabolism does not occur in an activity dependent manner, and that lactate is the preferred neuronal substrate. Contrary to this however, it is now well established that glucose transporters are present in neuronal membranes, indicating that they have the potential to transport and metabolise glucose [36, 37]. Moreover, studies have shown that whilst there is significant intracellular production of lactate in the brain, lactate uptake remains relatively slow. This is in opposition with the theory of lactate being used as a major neuronal fuel source [38]. The astrocyte-neuron lactate shuttle hypothesis, originally hypothesised by Pellerin and Magistretti, [39], states that neurons stimulate glycolysis in astrocytes through glutamate release. Uptake of synaptic glutamate from the neuronal synapse by astrocytes activates Na+/K+ ATPase’s due to the increased cellular uptake of Na+ which is co-transported

with glutamate and consumes the ATP produced by phosphoglycerate kinase [39]. This triggers astrocyte glucose uptake via GLUT1, and concomitantly glycolysis which produces pyruvate that is converted to lactate via lactate dehydrogenase (LDH). Lactate is transported out of cell via monocarboxylate transporter 1 (MCT1) and taken up by neurons via MCT2. LDH converts this back to pyruvate for re-entry into the TCA cycle via acetyl CoA [40] (Fig 1). In this way lactate can contribute to the activity-dependent energy demands associated with neuronal synaptic transmission [41]. Glutamatergic stimulation of astrocytic lactate production has been recently challenged due to the fact that; significant lactate oxidation has not been shown during brain activation, glial glutamate transporter GLAST forms a macromolecular complex linking glutamate uptake with its oxidation and as previously mentioned, neurons express glucose transporters and both take up and metabolise glucose [36, 42-44].

1.5 Astrocyte metabolic fuel storage

Glycogen is one of the major fuel sources for both astrocytes and neurons in the human CNS and is stored when glucose is in excess. Interesting recent findings have shown that high glucose exposure in astrocytes can lead to increased glycogen storage but at the expense of decreased mitochondrial and glycolytic capacity when subsequently metabolically stressed [16]. This has implications for neurodegenerative disorders with a significant astrocyte metabolic phenotype including amyotrophic lateral sclerosis (ALS). The data suggest astrocytes under metabolic stress have less capacity to sustain energetic cellular requirements, which would impact the ability of astrocytes to metabolically support neurons for example and is aligned with data produced from our laboratory [19].

Astrocytic glycogen that is concomitantly utilised by neurons, has been proposed to be a store for lactate, rather than glucose, which (as described above) could potentially supply the needs of nearby CNS cell populations [37, 45, 46]. As well as glycogen, astrocytes synthesise and release various lipid moieties including sterols, fatty acids and triglycerides as well as storing

phospholipids and sphingolipids in the plasma membrane [47-51]. Neurons do not store glycogen and synthesise lipids less efficiently than astrocytes [52]. Therefore, neurons take up astrocyte-derived lipids in order to support the formation and function of the synapses [53]. There are a variety of lipid classes in astrocytes that play multiple roles in astrocyte function, the intracellular localisation of these lipid classes are highlighted in Figure 1 with new insights discussed in the following section.

2. Lipids in Astrocytes

2.1. Cholesterol

Cholesterols are the major form of sterol lipid in the brain. Whilst the majority of sterol synthesis occurs in oligodendrocytes in the developing brain and is associated with myelin production [54], astrocytes are considered to be the main net producer of cholesterol in the CNS. Conversely, neurons are considered to be the net consumer [52]. Astrocyte cholesterol metabolism is independent of the rest of the cholesterol metabolism in the body, due to the presence of the BBB [55]**.** Cholesterol is one of the most important molecules of the synaptic membrane, in which it regulates a multitude of biochemical processes including membrane fluidity and ion channel function [53]. Of all the lipids present in astrocytes, cholesterol may have the most important role in astrocyte structure. Cholesterol helps regulate cell membrane flexibility, through interactions with nearby phospholipids [56]. Other important roles for cholesterol have also been identified, including lipid raft formation, glucose transport and inflammatory signalling [57-59]. Up to 70% of cholesterol is synthesised *de novo* in hepatic cells in the liver, with the remaining being derived in the intestines from dietary intake. This cholesterol is then circulated to all areas of the body via lipoprotein lipid-transfer.
The BBB, however, allows only High Density Lipoproteins (HDL's) to enter the brain: as a result, lipoproteins found in the brain must have been produced in the CNS. Brain cholesterol is

therefore believed to be synthesised *de novo* [60] and is considered the most cholesterol rich organ, accounting for around 25% of the total cholesterol content in the body. Estimates based on mouse models of the CNS suggest 80% of cholesterol is contained in myelin sheaths [54]. Nieweg *et. al*. [52] demonstrated that astrocytes primarily synthesise cholesterol via the Block pathway, and neurons via the Kandutsch-Russell pathway. In addition, cholesterol levels are higher in astrocytes with lower expression of cholesterol synthesising enzymes in neurons, suggesting neurons derive cholesterol externally [52]. Astrocytes are therefore believed to be the main site of cholesterol synthesis, which is an ATP-dependent process that occurs in the endoplasmic reticulum (ER) [61]. Cholesterol is then rapidly shuttled to the plasma membrane in vesicular and protein-mediated transport systems. Astrocytes also synthesise lipoproteins and Apo-lipoproteins for cholesterol transport [62]. Cholesterol-carrying lipoproteins cannot cross the BBB to enter the brain readily [63], highlighting the importance of astrocyte-derived cholesterol synthesis for glia and neurons. The significance of cholesterol synthesis in astrocytes has been demonstrated in studies investigating sterol regulatory element binding protein 2 (SREBP2), a transcription factor for several genes involved in sterol synthesis [48, 53, 64]. Astrocyte-specific depletion of SREBP2 produced profound effects in mice brains, such as reductions in neurite outgrowth, brain size and brain mass. Additionally, changes in liver mass, physical activity, motor coordination, memory and a shift towards carbohydrate metabolism were also observed. Reductions in brain cholesterol synthesis have been demonstrated in insulin-deficient mice [64]. These changes suggest astrocyte cholesterol synthesis may have an important role in metabolic disorders.

In addition to its role in membrane structure, cholesterol has also been shown as an important regulator of the activity and localisation of a range of membrane proteins [59, 65]. Membrane regions enriched with cholesterol and sphingolipids form lipid rafts and are understood to be a key regulator of activity of several membrane proteins [57]. An example of this is Toll Like Receptor 4 (TLR4), a receptor that promotes inflammation. Dimerisation of TLR4 is essential for

its activation and occurs largely in cholesterol-rich membrane regions [66, 67]. In addition to receptors, membrane transporter protein levels can also be influenced by the cholesterol content of membranes. Depletion of membrane cholesterol leads to increases in GLUT1 trafficking to the membrane, which is accompanied by an increase in glucose transport [58]. In our laboratory we coined the phrase metabolic flexibility, in relation to the ability of astrocytes to mobilize and catabolise alternative energy substrates to meet bioenergetic demand [18]. We proposed that a contributing mechanism to reduced metabolic flexibility observed in astrocytes derived from ALS patients was impairment of the transport of metabolic substrates across membranes. We surmised this was linked to alterations in cholesterol levels as energy production in the presence of mitochondrial specific substrates was reduced in ALS astrocytes compared to controls. However, treatment of astrocytes with saponin which binds to cholesterol to permeabilize membranes, restored mitochondrial substrate energy production in ALS astrocytes to levels comparable with control astrocytes. Cholesterol levels have previously been implicated in ALS, with increasing evidence emerging that cholesterol levels are lower in ALS patients [68, 69] and that higher serum cholesterol may prolong survival in patients [70].

This emerging area of study requires more mechanistic research into the role of membrane cholesterol and of metabolic substrate transport. However, therapeutic targeting of this pathway could enhance astrocyte metabolic flexibility and increase metabolic support to neurons which has the potential to modify disease progression in many neurodegenerative disorders.

2.2. Sphingolipids

Sphingolipids are a class of lipids characterised by the presence of a sphingosine backbone. This includes a range of lipids including ceramide, sphingosine and sphingomyelin. A range of different cellular functions for sphingolipids have been described. Sphingolipids are a key structural component for membranes, including lipid rafts [57]. Metabolites of sphingolipids have recently been identified as important regulators of inflammation, autophagy, cell growth and survival [71-

73]. For an extensive recent review of sphingolipids, see Hannun and Obeid [74] and for a review of sphingolipids in the nervous system, see Schnaar et al [75]. Several roles of sphingolipids in astrocyte function have also been described, including inflammatory regulation [76]. Numerous changes to sphingolipid structure and metabolism have been described in astrocytes from patients with various neurodegenerative diseases [48, 77-79] and will be discussed later in the article. Modifications to ceramide sphingolipids such as glycosylation to produce gangliosides, have already been associated with neurodegeneration [80-83]. Membrane ganglioside interactions with amyloid beta accelerate plaque formation in AD [84, 85] and inhibits alpha-synuclein fibrillation [86, 87]. Antibody-mediated ganglioside clustering can activate signalling pathways that inhibit neurite outgrowth [88, 89]. Sphingolipids are heavily enriched at synapses, and production is required for regulation of synapse structure and output [90]. It is currently hypothesised that normal production of gangliosides by astrocytes also enhances neurite outgrowth, regulates neuronal inflammation and stabilises neuron-glia interactions [83]. These findings highlight the importance of sphingolipids in the functioning nervous system, and necessitate further work to understand their use as potential therapeutic targets for nervous system disorders.

2.3. Phospholipids

Phospholipids are a vital component of cell membranes, making up the majority of the "phospholipid bilayer". As with other lipids mentioned, phospholipids are also synthesised heavily in the brain [91]. There are several classes of phospholipids, including phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and phosphatidylinositol. For a recent review of these lipids in the brain, see Tracey *et al*, [5]. In addition to their importance in cellular structure, exposure of neural cells to different phospholipids influences cell fate. Acting through the MAPK/ERK pathway, treatment of neural cells (including post-mitotic cells) with phosphatidylethanolamine, increased differentiation of cells into astrocytes [92]. In contrast,

phosphatidylcholine treatment reduced astrocyte differentiation. Phosphatidylethanolamine can bind to phosphatidylethanolamine binding protein (PEBP1) which can inhibit the MAPK/ERK pathway [93], suggesting the lipid may act by binding to PEBP1 and preventing it from inhibiting the MAPK/ERK pathway (Fig 2).

2.4. Free fatty acids

Free fatty acids, also known as Non-Esterified Fatty Acids are fatty acid molecules that are not bound to glycerol. Effects of exposure of astrocytes to free fatty acids are beginning to be characterised, with current evidence showing their ability to modulate inflammation. When treated with saturated fatty acids such as palmitic acid, an increase in pro-inflammatory cytokine production by astrocytes has been observed [94]. Several mechanisms have been proposed for this in astrocytes including increased ceramide production and activation of p38 or p42/44 MAPK pathways [94, 95]. In cells such as macrophages, palmitic acid has been identified as a TLR agonist, and can increase ROS production through mitochondrial complex I/III inhibition [96-98]. Conversely, polyunsaturated fatty acids (PUFA's), such as the omega-3 fatty acid docosahexaenoic acid (DHA), are increased in astrocytes during inflammation including palmitate-induced inflammation, suggesting that DHA may have anti-inflammatory properties [94, 99, 100]. Moreover, in microglia, DHA treatment inhibits NF-kB signalling, concomitantly increasing ROS production, leading to raised expression of HO1 via Nrf2 activation [100, 101]. *In vivo* models and human plasma analysis in ALS patients suggests gender-specific effects of DHA exists: DHA levels are raised significantly in men but not women, and DHA supplementation increased survival in male SOD1-ALS mice, but not females [102, 103]. Further characterisation of gender-specific differences in responses to DHA could help identify its effectiveness as a potential treatment for diseases such as ALS or AD, both of which feature inflammation as a pathogenic mechanism.

In addition to *in vitro* studies, astrogliosis has been documented extensively in rodent models in response to a high fat diet (HFD) in a range of brain structures, including the nucleus of the solitary tract, hypothalamus and substantia nigra [104-108]. Studies have documented the appearance of astrogliosis over a range of time periods: from acute 12hr responses [109] to 5 months after initiation (chronic) [108], although astrogliosis is usually more subdued after chronic HFD exposure. The significance of this astrogliosis response to a HFD has been investigated in connection to feeding behaviour of mice. Astrocyte-specific inhibition of NF-kB signalling to prevent astrogliosis, produced a 15% higher caloric intake in mice after acute HFD feeding [106]. Chronic HFD feeding caused glial ensheathment of pro-opiomelanocortin (POMC) synapses, potentially reducing inhibitory appetite signalling [104]. Taken together, these findings suggest exposure to elevated fatty acid levels after a HFD can induce astrogliosis, which has a role in maintaining energy homeostasis and may become dysregulated during chronic HFD exposure (Fig. 3). Targeting hypothalamic astrogliosis during obesity may restore appetite signalling and normal energy homeostasis.

In addition to membrane structure, inflammatory regulation and regulation of cell fate, astrocyte transport of lipids to neurons for use in metabolism is a crucial part of the astrocytic-neuronal communication axis. As astrocytes allow neurons to access their cellular resources, this enables metabolism to be maintained throughout higher levels of neuronal activity [8] which is crucial in both physiological and pathological conditions.

3. Lipid metabolism and storage in astrocytes and its role in neuron-astrocyte crosstalk

Current findings continue to highlight the importance of astrocytes in the maintenance of brain homeostasis, with an increasing focus on the ability of these cells to influence neuronal function. Lipid metabolism is crucial to normal astrocytic function and therefore a key intermediate in

neuron-astrocyte crosstalk. The following section highlights recent findings regarding the role of lipid metabolism in astrocyte metabolic support of neurons, and the role of astrocyte lipid signalling in neuronal morphology and synaptic transmission

3.1. Fatty acid oxidation and Lipid Droplets

Lipid droplets (LDs) are a fundamental component of lipid metabolism in astrocytes. LDs are ubiquitous cellular organelles that regulate the storage and hydrolysis of fatty acids in eukaryotes, forming rapidly in response to increased fatty acid levels and *vice versa* when fatty acids are depleted [110]. LDs consist of a core of neutral lipids made up of mostly cholesteryl esters, triacylglycerol and ether lipid monoalk(en)yl diacylglycerol, surrounded by a monolayer of phospholipids and proteins [111-113]. Though the process isn't fully elucidated it is thought LDs form in a triphasic process in the ER (Fig.4). Initially, fatty acids are nucleated, then undergo a growth phase after which they bud off and enter the cytosol. This theory has been supported by cryoelectron microscopy and immunocytochemical analysis [113, 114]. The droplets are then broken down by lipases via lipolysis, the rate limiting step of which is carried out by adipose triglyceride lipase [115]. The neutral lipids used in this process are derived from *de novo* synthesis from other fatty acids in the ER [116, 117]. In astrocytes, this may include excess fatty acids from neurons [8] and dietary fatty acids that cross both the BBB and astrocyte/neuron membranes via fatty acid binding proteins (FABPs) [118-120] (Fig. 4). FABPs are lipid chaperones in cells that regulate the response of lipids to stimuli. FABP7 is the major isoform in the brain, however, FABP3 and FABP5 are also expressed [121]. Astrocytic-FABP7 plays a role in dendritic morphology and synaptic transmission [122], sleep [123] schizophrenia [124] and Down syndrome [125].

The main purpose of LD generation is to provide fuel for β-oxidation. β-oxidation of LDs in the mitochondria provides an alternative energy generation pathway in times of starvation in several tissues, including astrocytes. Nutrient deprivation in rat primary astrocytes demonstrated β-

oxidation of LDs was crucial to the maintenance of cell viability during stress [126]. Moreover, inducing recurrent low glucose in human primary astrocytes led to a switch to fatty acid metabolism for energy production [127]. Evidence also suggest energy derived from β-oxidation in astrocytes metabolically supports neurons [8]. Furthermore, some argue that fatty acid oxidation (FAO) plays a more prominent role than that of a backup to glucose metabolism. Most reports consider glucose metabolism as the main or only method for metabolism in the brain [128]. However, it has been estimated upwards of 20% of energy generation in the brain is generated via FAO [129, 130]. Panov *et. al*. [128] argue FAO occurs concomitant with glucose metabolism based on the evidence that *in vitro,* astrocytes metabolise fatty acids alongside other metabolites. Eraso-Pichot *et. al*. [131] utilising bioinformatic analysis, showed an upregulation in FAO genes in human primary astrocytes. They also demonstrated FAO occurring in tandem with glycolysis *in vitro*, suggesting a precedent for FAO in the brain. FAO of LDs plays an undeniably important role in maintaining astrocyte-neuron homeostasis and further research stands to only emphasise this.

3.2. Astrocyte Lipid Signalling

3.2.1 Neuronal Morphology

Studies suggest that astrocyte-neuron crosstalk goes beyond providing metabolic support. Emerging evidence demonstrates astrocyte signalling and lipid metabolism mediates neural circuit function and formation. One example of this is in neural circuit outgrowth, a process which is known to be influenced by astrocytes [132]. Recent evidence suggests this process is carried out via the action of phosphatidic acid (PA) [133]. PAs are phospholipids important for signalling and activation of lipid-gated ion channels [134] and have long been linked to neurite outgrowth [135, 136]. PAs are synthesised by phospholipase D1 (PLD1) and 2 (PLD2) which

hydrolyse phosphatidylcholine to form PA and choline [137] and diacylglycerol kinase (DGK) [138] which phosphorylates diacylglycerol (DAG) to produce PA. This process is important for both astrocytes and neurons; in neurons DGK knockout attenuates synaptic vesicle recovery at the presynaptic terminal [139], PLD1 dysfunction is linked to impaired neurite outgrowth in Alzheimer's [140] and PLD2 ablation rescues synaptic function [141]; and in astrocytes, knockout of PLD1 and 2 reduces astrocyte proliferation in culture [142]. Zhu *et. al*. [133], demonstrated that when PLD1 was knocked down or inhibited in rat hippocampal astrocytes in co-culture with neurons, neuronal dendritic branching reduced significantly. PA addition restored dendritic branching and increased dendritic outgrowth. Furthermore, astrocyte conditioned media recapitulated these effects, demonstrating that PLD1 dendrite outgrowth was mediated by PA generation and release from astrocytes. It is possible the process may regulate secretion of extracellular vesicles as these processes are known to affect morphology of neurons amongst other roles [143]. Inhibition of protein kinase A (PKA) reduced PA-stimulated dendritic outgrowth, but not fully, suggesting PKA signalling, which has been shown previously to influence dendrite outgrowth [144] was not the sole mechanism by which PA influences neurite outgrowth. PLD1 has also recently been shown to affect protein kinase-D1 which affects dendritic spine morphogenesis; thus this could be another area of influence for astrocytic PA [145].]. Therefore, astrocyte PA clearly has an important role in shaping neuronal morphology.

3.2.2. The endocannabinoid system and the neuronal synapse

The endocannabinoid (ECB) system is made up of G-protein-coupled cannabinoid receptors (CBRs) that are activated by ECBs, lipid-based eicosanoid neurotransmitters such as anandamide and 2-arachidonoylglycerol (2-AG) [146, 147] . The system has regulatory roles in heart, liver and brain function and has been widely studied for its potential role in astrocyte-neuron communication [148, 149]. ECBs are synthesised generally in response to G-protein

coupled receptor activation or depolarization, with 2-AG being synthesised from diacylglycerols (DAGs) by DAG lipases and phospholipase C [150, 151] whilst anandamide is synthesised from N-acyl-phosphatidylethanolamine by PLD [152]. Two CBRs have been characterised in the human body, CBR1 [153] and CBR2 [154]. CBR1 is highly expressed in the brain where it mediates most notably mood, cognitive ability, appetite and the pharmacological effects of cannabis, and is highly important for the control of synaptic transmission. Navarette and Araque [148], showed depolarization in pyramidal neurons of the rodent brain leads to ECB release, activating astrocyte CBR1 receptors triggering phospholipase-C dependent Ca^{2+} release from astrocytes. This stimulated glutamate release, activating N-methyl-D-aspartate (NMDA) receptors in the pyramidal neurons. The same phenomenon has also been reported in the human brain [155].

Astrocytes also influence long-term changes in synaptic transmission. Spike-timing dependent plasticity is a process in which neurons adjust the strength of their signals dependent on the timing of input and output action potentials [156], which influences neuronal circuit development [157]. Min and Nevian [158], demonstrated that activation of astrocytic CBR1 receptors leads to a transient increase in Ca^{2+} levels and Ca^{2+} signalling. Subsequent astrocyte glutamate release then activates NMDA receptors which triggers ECB mediated spike timing-dependent long term depression (t-LTD), showing the vital role astrocyte-ECB interaction plays in t-LTD and thus neuronal development. More recent studies have also shown a contrary role for CBR1 in long-term potentiation (LTP). Mice with a CBR1 knockout demonstrate reduction in LTP at hippocampal synapses, whereas CBR1 receptor activation increased exogenous D-serine levels (which is needed for LTP [159]), thus CBR1 controls synaptic D-serine and therefore LTP [160].

The endocannabinoid system has also garnered recent attention because of its potential health benefits, with the UK government recently shifting cannabis-based products from schedule 1 to

schedule 2 in the Misuse of Drugs Regulations 2018. The most widely studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC works purportedly via activation of CBR1 [161, 162] whilst CBD has low affinity for CBRs, instead acting as an antagonist of CBR agonists [163]. Nabiximols (a.k.a. Sativex), a CBD/THC mix, purified from *Cannabis sativa L.* is prescribed as an analgesic [162, 164, 165], and alleviates the negative effects of cannabis withdrawal [166]; whilst Nabilone (a.k.a. Cesamet) and Dronabinol (a.k.a. Marinol®/Syndros) are synthetic cannabinoids that mimic THC and may be effective as antiemetic's [167, 168] and analgesics for diseases such as multiple sclerosis and fibromyalgia [169-171]. A recent meta-analysis of cannabinoids as therapeutics showed moderate support for the alleviation of chronic pain and spasticity, low support for cannabinoids as analgesics, and an increased risk of adverse events [172]. The suggestion that cannabinoids can treat mental disorders like anxiety and depression may also be misplaced as a recent review analysing the available literature on THC used therapeutically (with or without CBD) to treat mental disorders highlights [173]. Black *et al*. (2019) show only a few investigations report an improvement in anxiety in treated patients (but only in individuals with a pre-existing condition). No improvement was reported in other conditions (such as depression) though multiple studies highlight the increased risk of adverse events and adverse events due to withdrawal. Cannabinoids therefore have therapeutic potential, but further research, particularly concerning true efficacy and long-term effects are required and wide-spread use of cannabinoid-based therapies in the near future seems unlikely.

4. How defective lipid metabolism in astrocytes contributes to CNS disorders

In the previous sections we discussed for the most part the role of lipid metabolism in the physiological context. For the remainder of the review, we will discuss the new insights that have recently emerged linking disruption with astrocytic lipid metabolism and neurological disorders.

It is well established that metabolic dysfunction influences pathogenesis of a number of neurodegenerative disorders including ALS, PD and AD, for in depth reviews see [174-176]. The role of astrocytes in disease pathogenesis in ALS for example is well established with new astrocyte associated disease relevant pathways being recently identified using human models of disease combined with novel approaches such as phenotypic metabolic profiling [10, 18, 19]. The role of astrocytes in PD and AD is less well established but studies are emerging linking astrocyte metabolic defects with inflammation, BBB disruption and neuronal loss [177-181]. The role of lipid metabolism dysfunction as a whole in the CNS is outside the remit of this review article and has been covered by other authors in recent review articles [5, 182]. However, in this final section we will focus on the role of astrocytic lipid metabolism, signalling and inflammation in the context of CNS disorders and we will discuss the emerging role of manipulating astrocyte lipid metabolism as a therapeutic approach.

4.1. Astrocyte LDs in disease.

As previously mentioned, effective neuronal function is intrinsically linked to astrocyte metabolism and cross talk exists where oxidative stress in neurons triggers LD formation in nearby astrocytes which can lead to neurodegeneration via lipid peroxidation [6, 7]. This formation is dependent on Apo lipoproteins and the neuron-glial lactate shuttle [183]. Inhibition or deletion of glial and neuronal MCTs reduced LD accumulation in mouse glial-neuronal co-cultures and Drosophila respectively. Whilst inhibition of neuronal lactate production and fatty acid transport proteins had similar effects in flies. Recent work by Ioannou *et. al.* [8, 184] demonstrated that hyperactive neurons accumulate peroxidated lipids and expel them in association with APOE-positive lipid particles. These particles are then concomitantly endocytosed by neighboring astrocytes, which incorporate the lipids as droplets. Moreover during increased neuronal activity, astrocytes upregulate antioxidant genes and breakdown LDs to fuel oxidative phosphorylation. However, the precise role of astrocyte LDs is still unclear as

are the role of astrocyte LDs in neuroprotection or as a driver of neurodegenerative disorders [6, 185]. This is an avenue of research which is likely to attract a great deal of attention over the next few years due to the potential therapeutic benefits to multiple CNS disorders of understanding the associated mechanisms. For example, accumulation of LDs in astrocytes has recently been observed in murine models of ALS, and the role of LDs in motor neuron diseases has been recently reviewed [186]. Moreover, in AD it was found that astrocytes expressing the E4 APOE allele accumulated higher amounts of LD, and had both decreased fatty acid uptake and decreased fatty acid oxidation compared to E3 astrocytes. Furthermore, E4 astrocytes were more sensitive to carnitine palmitoyltransferase-1 inhibition than E3 astrocytes indicating a preference for mitochondrial fatty oxidation [187]. In a mouse model of Leigh Syndrome where the mitochondrial complex I component Ndufs4 was knocked out, neuronal mitochondrial abnormalities led to pre-symptomatic glial LD accumulation [6]. This highly significant study suggested that LD accumulation may represent an early indicator and/or promoter of neurodegeneration. Furthermore, targeted lipase overexpression or lowering ROS levels in Drosophila, reduced LD accumulation in glia, potentially delaying the onset of neurodegeneration [6]. FABPs are important for LD synthesis in response to reactive oxygen species. Knockout of FABP7 in primary mouse astrocytes caused reduced LD formation, increased ROS toxicity and impaired thioredoxin signalling in response to ROS induced stress, activating apoptosis signalling pathways. Conversely, overexpression of FABP7 in a human-glioma line increased LD accumulation and expression of antioxidant defence pathways [188], suggesting FABP7 protects astrocytes from oxidative stress via generation of LDs, which has implications for multiple neurological diseases with oxidative stress as a pathological mechanism.

4.2. Astrocyte lipid signalling and inflammation in disease

A mechanism of dysfunction exists between LDs and lipid signalling in the CNS. Lipoprotein lipase (LPL) is a serine hydrolase that releases free fatty acids from circulating triglyceride-rich lipoproteins and has previously been implicated in CNS metabolic regulation [189]. A recent study showed that LPL loss in mice hypothalamic astrocytes led to decreased LD content [47]. It was suggested that LPL mediates lipid partitioning and is needed for nutrient sensing and energy homeostasis regulation in the CNS. LPL deficient mice suffered glucose intolerance and weight gain when fed a HFD, as well as a compensatory upregulation of lipogenesis-related genes, glycolytic flux and ceramide.

Ceramide is an important multifunctional intracellular signaling molecule where alterations in levels have been linked to neurological diseases. Recently, a connection was suggested between ceramide levels and inflammation in frontotemporal lobar dementia (FTLD) patient astrocytes [79]. Moreover, in patients with Pick's disease, (a form of frontotemporal dementia), ceramide 16:0 levels were shown to be raised in astrocytes but not in other forms of glia, such as microglia. Although these lipids compose a small fraction of total ceramide from the membrane, increases in astrocyte ceramide 16:0 have previously been observed in active multiple sclerosis lesions (with increased acid sphingomyelinase expression), have been observed in AD patients and have been linked to increased apoptosis in cells [77, 78, 190]. These data in combination with the increase in ceramide and sphingosine-1-phosphate receptor 3 levels observed in astrocytes from patients with capillary cerebral amyloid angiopathy [191], potentially indicate a common pathogenic mechanism between neurological diseases.

As previously mentioned, dietary fatty acids have also been shown to modulate inflammation. Conjugated linoleic acid has been shown to alter the levels of TNF-α, IL-1β, and RANTES in cultured human astrocytes [192]. Within the context of ischemia, intravenous injection of α-lipoic acid reduced neuronal damage in a rat model of ischemia but did not reduce astrogliosis [193]. Whilst inhibition/deletion in mice of (seladin-1)3β-Hydroxysteroid-Δ24 reductase (DHCR24), (a

cholesterol biosynthetic pathway enzyme), led to increased ischemic lesion and inflammation after middle cerebral artery occlusion [194]. Loss of seladin-1/DHCR24 as observed in AD brains, decreased plasma membrane cholesterol levels and concomitantly the formation and stability of lipid rafts. In mice, loss of seladin-1/DHCR24 led to a decreased association of the glutamate transporter EAAT2 with lipid rafts and decreased glutamate uptake in astrocytes. These data indicate that DHCR24 mediated lipid raft integrity plays a crucial protective role in the ischemic brain by guaranteeing EAAT2-mediated uptake of glutamate excess. These highly significant results link cholesterol, inflammation and lipid raft integrity to EAAT2-mediated uptake of glutamate excess via seladin-1/DHCR24. This has implications for a variety of neurological disorders including ischemia, AD and ALS with similar pathways observed in psychiatric disorders.

4.3. Is astrocyte lipid pathway manipulation beneficial in neurological disorders?

The synaptic phospholipid, lysophosphatidic acid (LPA), has been shown to regulate cortical excitation/inhibition balance and sensory information processing [195-197]. In a recent study, the LPA-synthesizing enzyme autotaxin (ATX) which is expressed in the astrocytic compartment of excitatory synapses modulating glutamatergic transmission was found to be sorted to excitatory not inhibitory synapses [198]. This sorting was regulated by neuronal activity via astrocytic glutamate receptors. Therefore, pharmacological ATX inhibition has been proposed as a method to reverse cortical hyperexcitability in schizophrenia, suggesting that manipulating astrocytic lipid function may be a viable therapeutic approach in neurological disorders. But is that the case?

The ability to manipulate catabolic pathways to increase carbon flow through those pathways or to mobilise internal energy stores such as fatty acids in times of bioenergetic need may be a viable metabolic based therapeutic approach. Catabolic manipulation ties into the concept of

metabolic flexibility mentioned previously and theoretically would not only be beneficial for astrocyte bioenergetic function, but also for the ability of astrocytes to support neuronal function in times of stress [18, 19]. With this in mind oleoylethanolamide (OEA), a bioactive lipid mediator produced by glial cells after tissue damage has been shown to upregulate PPAR-α in TGF-β1 treated astrocyte C6 cells [199]. These data indicate that OEA may attenuate astrocytic scar formation and improve motor function after ischemic stroke. Fatty acid supplementation may also be beneficial in reducing astrocyte activation and inflammation in PD. 6-hydroxydopamine treated male rats supplemented with omega-3 polyunsaturated fatty acids showed reduced GFAP and iNOS staining in the striatum and substantia nigra pars compacta indicating a reduction in the inflammatory profile in these animals [200]. Enhancing FAO in astrocytes using a synthetic peroxisome proliferator activated receptor delta agonist GW0742 may also have therapeutic potential in AD [201]. iPSC astrocytes generated from AD patients with a FAO defect showed an increase in carnitine palmitoyltransferase-I-a expression and FAO capacity when treated with GW0742. Similar effects in FAO were observed using GW0742 in the amyloid precursor protein/ presenilin 1 AD mouse model as well as reversed memory deficits, increased neurogenesis and reduced cortical inflammatory genes. However, in iPSCs, GW0742 did not protect against pro-inflammatory activation and in the mouse model, astrogliosis was unaffected, indicating that increasing FAO does not reverse the metabolic deficit fully. This may be because astrocyte metabolic adaptation to fatty acid dependent respiration in times of glucose hypometabolism (as observed in AD for example [21] comes at a cost. Recent work in primary astrocytes has suggested that glucose starvation leads to activation of 5' adenosine monophosphate-activated protein kinase. This causes a concomitant upregulation of uncoupled, fatty acid dependent mitochondrial respiration with reduced coupling efficiency [127], potentially leading to enhanced oxidative stress. With these data in mind and in combination with the earlier discussion around the links between certain fatty acids and inflammation, careful

mechanistic analysis must be performed to fully elucidate the action of any potential lipid based metabolic interventions including high fat diets.

5. Conclusions

Astrocytes play a key role in the CNS from maintenance of the BBB, cell to cell communication and maintenance of metabolic homeostasis. Astrocyte lipids play a crucial role in these functions from maintaining membrane flexibility, reducing inflammation and influencing organelle structure and intracellular signalling. The differential use of lipids in astrocytes compared to, for example neurons, plays a key protective role in the CNS. This review article has summarised the current, ongoing research in the area of astrocyte lipid metabolism and contextualized those findings with historical scientific research in the CNS. We have highlighted throughout, key emerging areas in lipid function in astrocytes and the importance of these pathways in both health and disease and also astrocyte metabolic function as a whole. The emerging field of astrocyte LD storage has revealed the links between astrocyte lipid metabolism, oxidative stress, metabolic function, lipid signaling and anti-inflammatory pathways. Disruption in these pathways can alter the metabolic balance in the CNS causing energy generation dysregulation, inflammation, excitotoxicity and toxicity, which are pathogenic mechanisms relevant to many neurodegenerative disorders including ALS, PD, AD and ischemic stroke to name a few. Further characterisation of the pathways in health and disease will aid the understanding of the mechanisms behind these pathogenic mechanisms and will identify novel therapeutic targets or nutritional supplementation strategies to help ameliorate the dysfunction and benefit patients.

Author contributions

J.A.K.L., B.H., J.A., R.A., and S.P.A., wrote the manuscript and designed the figures**.**

Declaration of Competing Interest

The authors are not aware of any conflicts of interest that may affect the objectivity of this review.

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Figure Legends

Figure 1. Intracellular lipid localisation in astrocytes and astrocyte-neuron communication.

Demonstrated is the intracellular localisation of sterol lipids (SL), phospholipids (PL), triacylglycerol's (TAG), fatty acids (FAs) and sphingolipids (SpL). **(A)** FAs are the precursor for most types of lipids (excluding sterol lipids) and are synthesised and stored in the cytosol (as shown). Sterol lipids, phospholipids and sphingolipids are important in maintaining astrocyte cell and organelle membranes including mitochondria and can be metabolised to produce regulatory molecules for intracellular processes. Triacylglycerol's are mainly synthesised and located in the endoplasmic reticulum (ER). Astrocytes metabolically communicate with neurons via monocarboxylate transporters (MCT1/2) including supplying neurons with lactate according to the lactate shuttle hypothesis. As shown, **(B)** an influx of glutamate into astrocytes, co-transported with Na^+ from the neuronal synapse, results in glucose uptake into astrocytes via Glut-1 receptors **(C)**. **(D)** Glucose is metabolised to pyruvate which either enters the mitochondria or **(E)** is dehydrogenated to lactate by LDH. **(F)** Lactate is then transported out of astrocytes via MCT1 receptors, and taken up by MCT2 receptors on neurons. **(G)** Lactate is then converted back to pyruvate via neuronal LDH (or glucose is taken up by Glut-3 on neurons and oxidised to pyruvate) where it can then enter the mitochondria and be converted to acetyl CoA.

Figure 2. Phosphatidylethanolamine promotes neural stem cell differentiation into astrocytes, whilst phosphatidylcholine inhibits differentiation to astrocytes.

Phosphatidylethanolamine (PtE) binds to phosphatidylethanolamine binding protein (PEBP), inhibiting its inhibitory action of mitogen-activated protein kinase (MAPK), which promotes differentiation into astrocytes. Phosphatidylcholine (PtC) exposure activates protein kinase A (PKA), which promotes differentiation into neurons and inhibits differentiation to astrocytes.

Figure 3. Schematic representation of the influence of different structural lipids on astrocyte function.

Saturated fatty acid exposure promotes astrogliosis by activation of mitogen-activated protein kinase (MAPK). During astrogliosis, PUFA production increases, leading to an increase in docosahexaenoic acid (DHA) extracellularly, which can inhibit astrogliosis. Sterol regulatory element binding protein 2 (SREBP2) promotes synthesis of cholesterol, that regulates lipid raft formation and inhibits glucose transporter 1 (GLUT1) translocation to the membrane. Astrocyte production of cholesterol and gangliosides promotes neuron outgrowth in nearby neurons. Changes to ceramide concentrations in astrocyte membranes observed in various neurological diseases implicate them in cellular functions such as inflammation and apoptosis.

Figure 4. Lipid droplet synthesis in astrocytes

Lipid droplet synthesis occurs in the ER in a triphasic process **(A)**: (i) Nucleation-neutral lipids accumulate in the ER bilayer (ii) Growth–LDs form into a sphere and are wrapped in the ER bilayer as neutral lipids accumulate (iii) Budding–LDs then bud off into the cytosol. Fuel for this synthesis comes in the form of FAs which are converted into neutral lipids in the ER. In astrocytes FAs for neutral lipid synthesis can come from the following sources: **(B)** Excess neuronal FAs - FAs complex with Apo-lipoproteins which are then shuttled to astrocytes and

broken down by lysosomes; FAs derived from this process subsequently enter the ER. **(C)** Dietary FAs- FAs from the diet cross the BBB by binding with FABPs that transport them through transporters such as CD36. LDs generated in the ER can then be metabolised by β-oxidation to provide metabolic support for neurons **(D)**.

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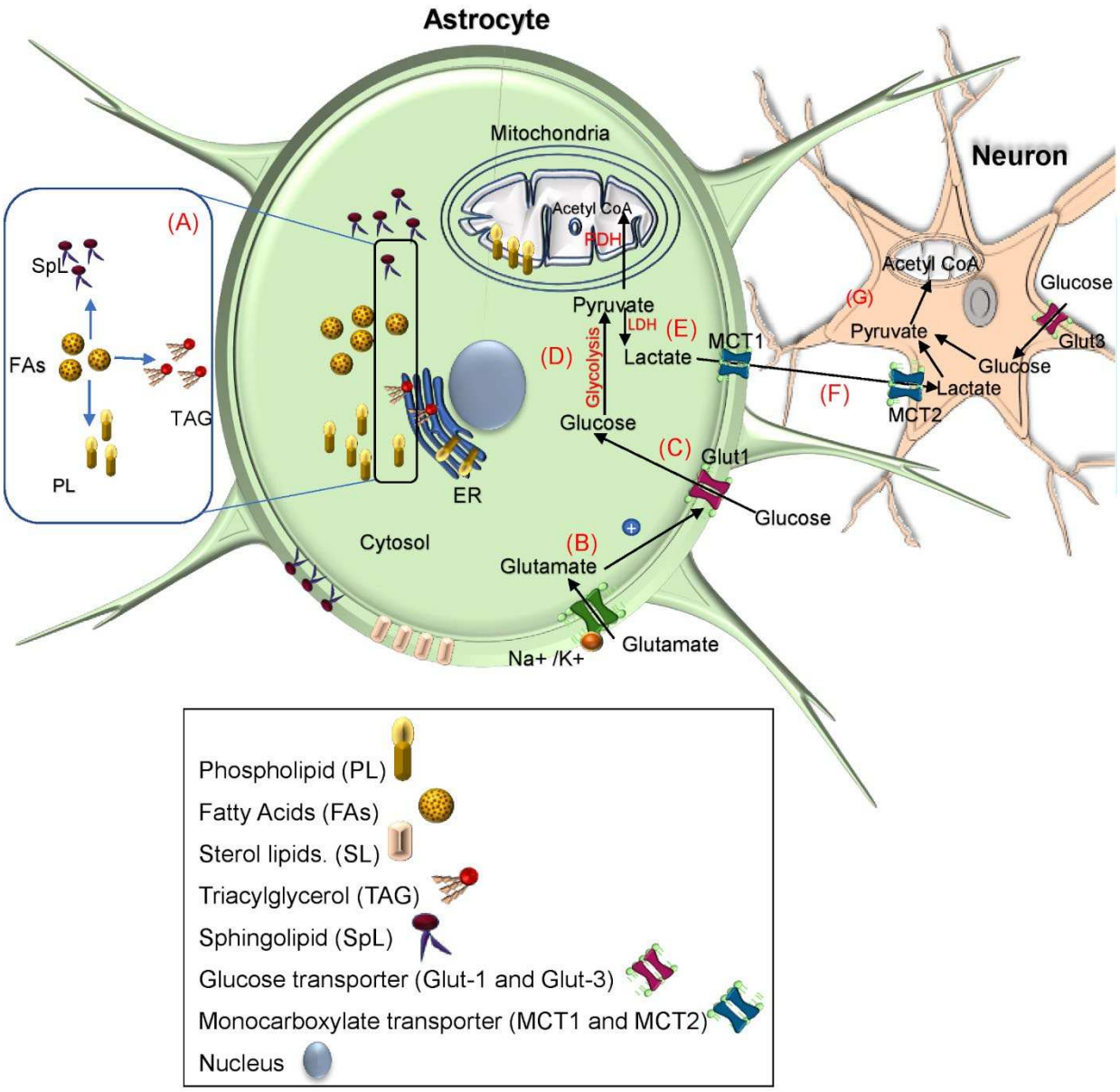
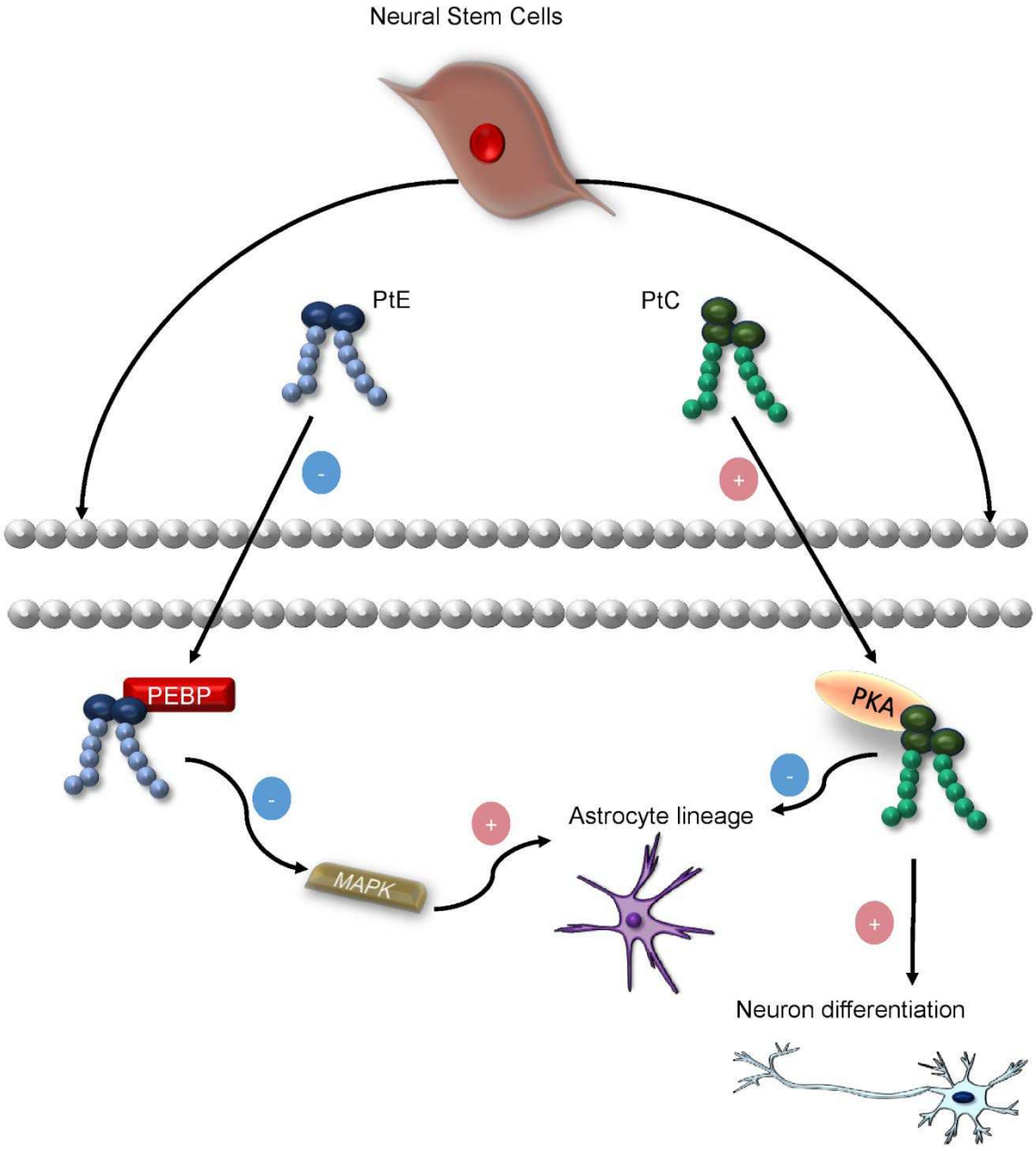
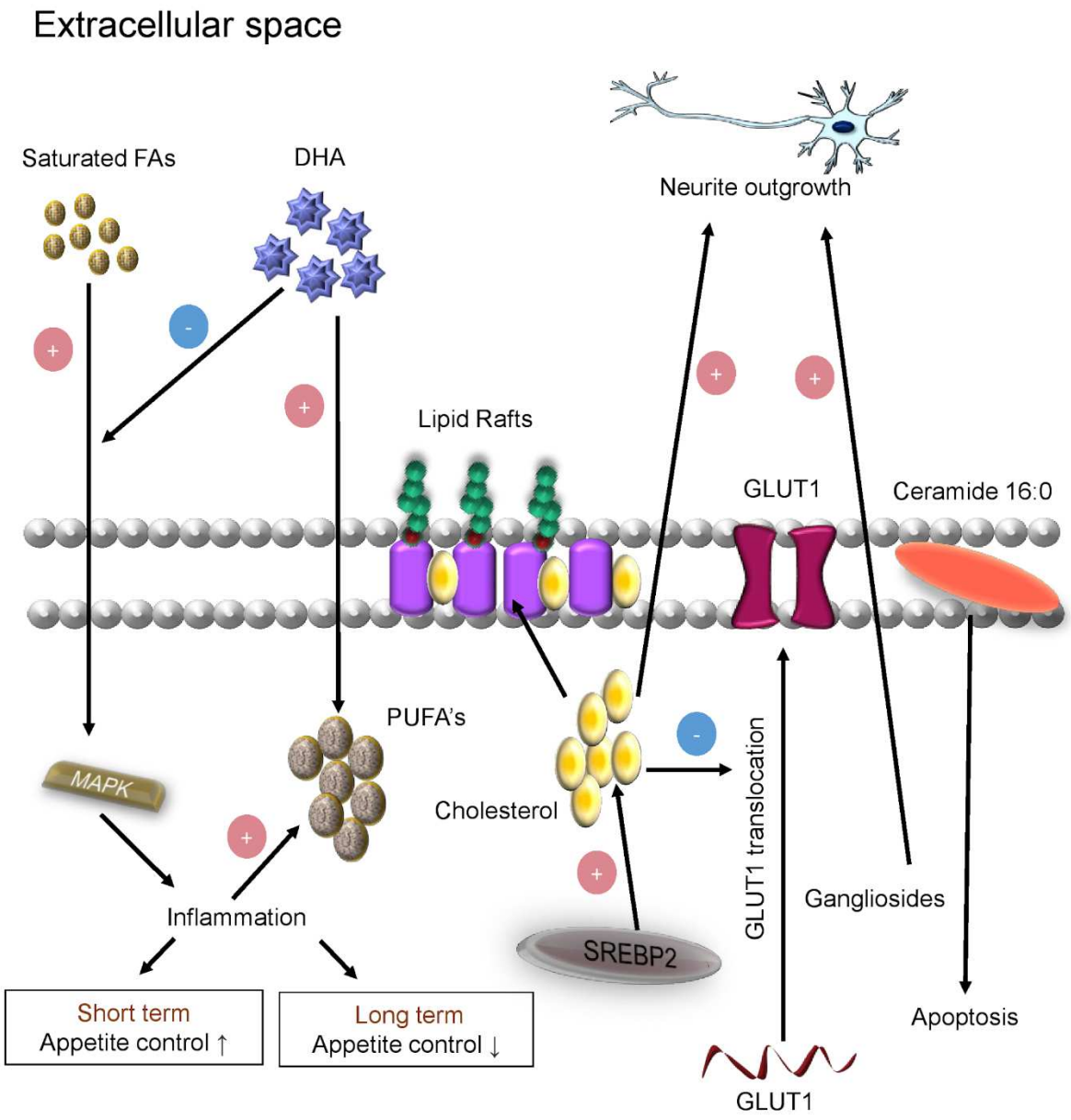
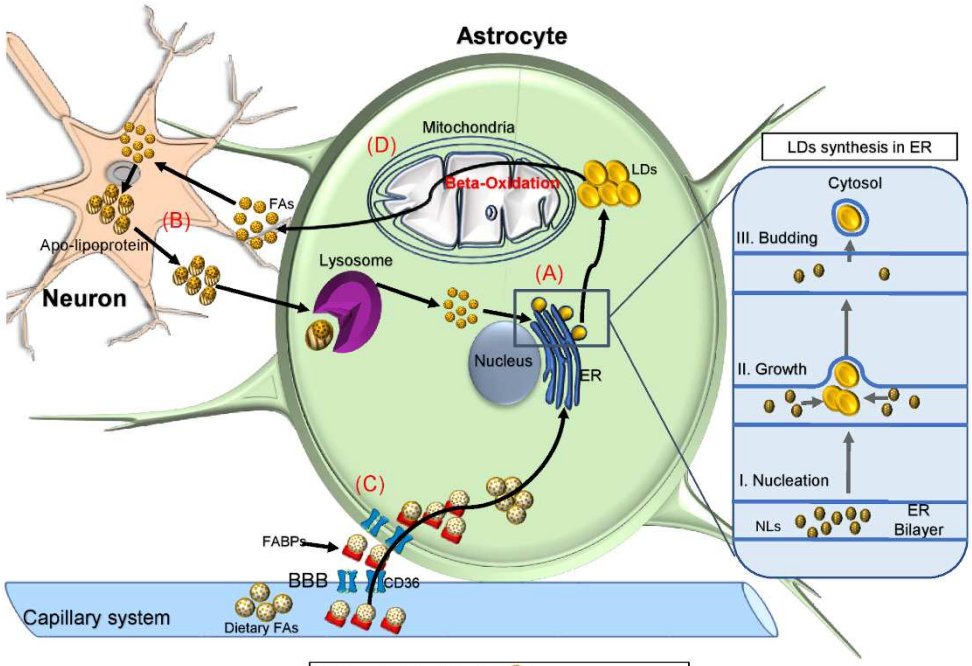

Astrocyte
Neuron
Mitochondria
Acetyl CoA
PDH
Pyruvate
LDH
(E)
Lactate
MCT1
(D)
Glycolysis
Glucose
(C)
Glut1
Glucose
(B)
Glutamate
Na+ /K+
Glutamate
Cytosol
ER
(A)
SpL
FAs
TAG
PL
(G)
Acetyl CoA
Pyruvate
Glucose
Glut3
Glucose
(F)
Lactate
MCT2
Phospholipid (PL)
Fatty Acids (FAs)
Sterol lipids. (SL)
Triacylglycerol (TAG)
Sphingolipid (SpL)
Glucose transporter (Glut-1 and Glut-3)
Monocarboxylate transporter (MCT1 and MCT2)
Nucleus


Neural Stem Cells
PtE
PtC
-
+
PEBP
PKA
-
-
+
MAPK
+
Astrocyte lineage
Neuron differentiation


Extracellular space
Saturated FAs
DHA
Neurite outgrowth
Lipid Rafts
GLUT1
Ceramide 16:0
PUFA's
MAPK
Cholesterol
GLUT1 translocation
Gangliosides
Inflammation
SREBP2
Short term
Appetite control ↑
Long term
Appetite control ↓
Apoptosis
GLUT1
Cytoplasm



Fatty Acids (FAs)

Dietary Fatty Acids (Dietary FAs)

Apo-lipoprotein

Lipid droplet (LD)

Fatty Acid binding protein (FABPs)

CD36

Neutral Lipids (NLs)