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REVIEW

Lipid droplets in the nervous system

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Lipid droplets are dynamic intracellular lipid storage organelles that respond to the physiological state of cells. In addition to controlling cell metabolism, they play a protective role for many cellular stressors, including oxidative stress. Despite prior descriptions of lipid droplets appearing in the brain as early as a century ago, only recently has the role of lipid droplets in cells found in the brain begun to be understood. Lipid droplet functions have now been described for cells of the nervous system in the context of development, aging, and an increasing number of neuropathologies. Here, we review the basic mechanisms of lipid droplet formation, turnover, and function and discuss how these mechanisms enable lipid droplets to function in different cell types of the nervous system under healthy and pathological conditions.

Introduction to lipid droplets

Lipid droplets are evolutionarily conserved organelles that dynamically stockpile fatty acids. During conditions of fatty acid surplus, lipid droplets store fatty acids in the form of neutral lipids, including triglycerides and cholesterol esters. This storage is essential for the timely release of fatty acids needed for cell signaling, lipid synthesis, and energy production (Walther et al., 2017; Cohen, 2018; Olzmann and Carvalho, 2019). The storage of neutral lipids in lipid droplets also protects cells from the buildup of cytosolic fatty acids that can be toxic (Unger and Orci, 2002). Fatty acid accumulation is associated with lipotoxicity (Listenberger et al., 2003), ER stress (Fu et al., 2011; Velázquez et al., 2016), and mitochondrial damage and dysfunction (Nguyen et al., 2017). Therefore, balanced lipid storage in lipid droplets is essential for organismal health.

The health and function of the nervous system is intimately tied to lipid homeostasis. This is not surprising considering the brain is composed of nearly 60% lipid by dry weight, making it the second fattiest tissue in the body, behind adipose tissue (O'Brien and Sampson, 1965). While alterations in lipid homeostasis are well studied in many neuropathologies (Alecu and Bennett, 2019; Chang and Chang, 2017; Karasinska and Hayden, 2011), the appearance and function of lipid droplets in the brain have only recently gained attention. It is now known that lipid droplets are present in cells of the nervous system during early development, aging, and neuropathologies (Bailey et al., 2015; Farmer et al., 2020; Ioannou, 2020; Marschallinger et al., 2020). In this review, we briefly introduce the mechanisms of lipid droplet formation and regulation (Fig. 1) and the various cell types in the brain in which they form. We then focus on various neuropathologies where lipid droplets have been reported and outline outstanding questions in the field related to lipid droplets in the brain.

Lipid droplet biogenesis

Lipid droplets are composed of a hydrophobic core of neutral lipids, mainly triglycerides and cholesteryl esters, surrounded by a phospholipid monolayer decorated with proteins known to regulate lipid droplet function (Fig. 1 A). Lipid droplet biogenesis is a multistep process involving neutral lipid synthesis at the ER membrane, emergence and budding of nascent lipid droplets, and their continued growth via fusion and incorporation of additional neutral lipids (Fig. 1 B). Several excellent reviews have been written to detail the mechanisms and protein players involved in each step of lipid droplet biogenesis (Olzmann and Carvalho, 2019; Cohen, 2018; Pol et al., 2014; Wilfling et al., 2014). Of the central enzymes responsible for lipid droplet biogenesis, diacylglycerol acyltransferases (DGATs) catalyze the final step of triglyceride synthesis. This makes them useful targets to modify lipid droplet formation, including in studies of the nervous system (Yang et al., 2020; Inloes et al., 2014; Cheng et al., 2020). The two mammalian DGATs, DGAT1 and DGAT2, localize to the ER, where they largely carry out the same biochemical reaction, the conversion of diacylglycerol to triacylglycerol. In addition to the ER, DGAT2 localizes to lipid droplets during their growth (McFie et al., 2011; Kuerschner et al., 2008; Stone et al., 2009; Chitraju et al., 2017; Cases et al., 2001). As those studies were performed using overexpressed protein, the field would greatly benefit from endogenous tagging of these enzymes to study their localization in different cell types. Regardless, DGATs play an important functional role in regulating cell physiology, including within the nervous system.

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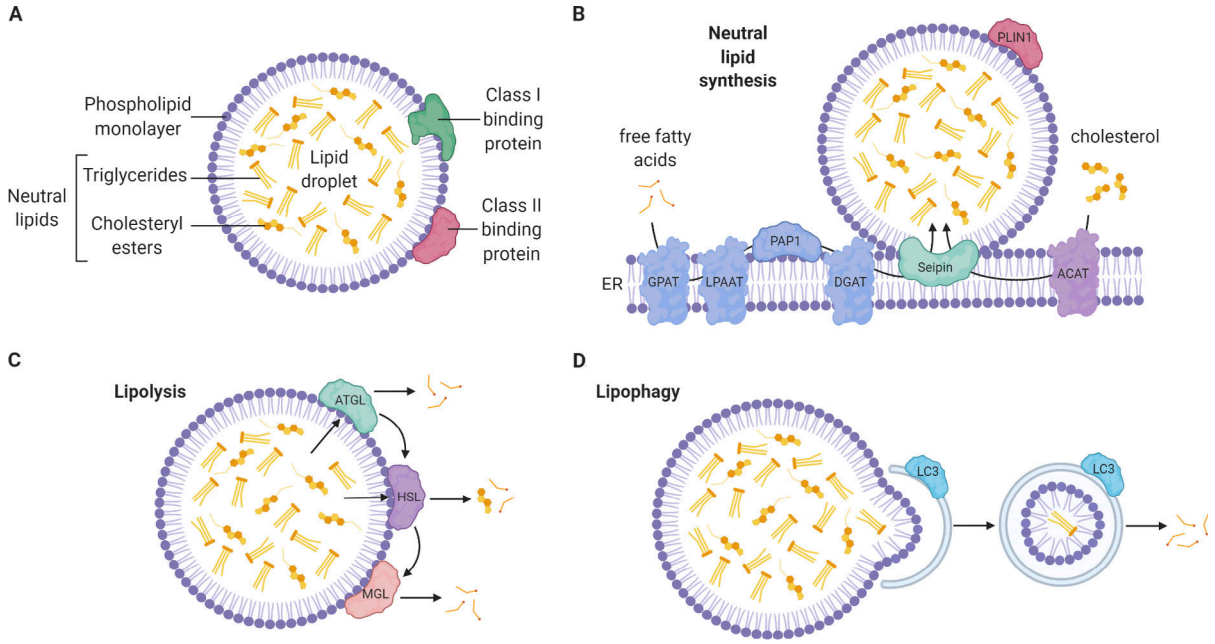

Figure 1. **Schematic of lipid droplet formation and turnover.** Reviewed in more detail in Olzmann and Carvalho (2019) and Walther et al. (2017). **(A)** Structure of a lipid droplet including two classes of binding proteins. Class I proteins, via their hydrophobic hairpin, insert into the phospholipid monolayer, while class II proteins bind to the surface of lipid droplets through an amphipathic helix or stretch of hydrophobic residues. **(B)** Neutral lipid synthesis. Free fatty acids and cholesterol are converted to triglycerides and cholesteryl esters, respectively, between the leaflets of the ER membrane and enter lipid droplets. Important enzymes in the process include glycerol-3 phosphate acyltransferase (GPAT); lysophosphatidic acid acyltransferase (LPAAT), also known as 1-acylglycerol-3-phosphate *O*-acyl-transferase (AGPAT); phosphatidic acid phosphatase (PAP1); diacylglycerol acyltransferase (DGAT); and acetyl-CoA acetyltransferase (ACAT). Seipin localizes to the ER–lipid droplet interface to facilitate lipid flow into lipid droplets. Lipid binding proteins such as perilipin-1 (PLIN1) prevent lipases from hydrolyzing neutral lipids, thereby promoting lipid droplet growth. **(C)** Lipolysis involves the hydrolysis of neutral lipids back into free fatty acids and cholesterol and their release into the cytosol. Important enzymes in the process include adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL). **(D)** Lipophagy involves the autophagic degradation of lipid droplets and involves machinery common to macroautophagy such as microtubule-associated proteins 1A/1B light chain 3B (LC3). Hydrolysis of neutral lipids by lysosomal lipases liberates free fatty acids and cholesterol.

Suppression of DGATs promotes axon regeneration in neurons following injury by redirecting fatty acids from neutral lipid to phospholipid synthesis (Yang et al., 2020). DGAT1 is also required for preventing lipotoxicity, mitochondria dysfunction, and ER stress during lipolysis (Chitraju et al., 2017; Nguyen et al., 2017). As these cellular insults commonly occur in the brain during pathology, DGATs, and therefore lipid droplet formation, could play a similarly protective role in the brain.

Regulation of lipid droplet formation and function

Lipid droplet formation is tightly associated with the nutrient status of cells. Lipid droplets form in response to high availability of exogenous lipids. This can be observed in vivo with a high-fat diet and in cultured cells treated with lipids (Cao et al., 2019; Soayfane et al., 2016; Krahmer et al., 2011; Kwon et al., 2017). Conversely, lipid droplets also form under nutrient deprivation (Rambold et al., 2015; Seo et al., 2017; Hariri et al., 2018). This occurs as cells shift their energy source from glucose to high-energy fatty acids to boost ATP production via mitochondrial fatty acid catabolism (Gerhart-Hines et al., 2007). The formation of lipid droplets under starvation requires autophagic breakdown of membranes, which supplies lipid droplets with fatty acids that will be stored until they are ready to be catabolized in the mitochondria (Rambold et al., 2015).

In addition to nutrient status, lipid droplet formation is induced by cellular stress. This includes mitochondrial dysfunction (Boren and Brindle, 2012; Lee et al., 2013), ER stress (Fei et al., 2009; Chitraju et al., 2017; Velázquez et al., 2016), hypoxia (de la Rosa Rodriguez et al., 2021; Bildirici et al., 2018), and inflammation (Karagiannis et al., 2020; Koliwad et al., 2010). There are several proposed functions for lipid droplet formation during cellular stress. Lipid droplet formation can buffer specific types of fatty acids. During hypoxia, for example, overproduction of saturated fatty acids generates ceramides and acylcarnitines that lead to lipid-mediated toxicity and apoptosis (Young et al., 2013; Kamphorst et al., 2013; Nguyen et al., 2017). The formation of lipid droplets reduces this saturated fatty acid buildup in the cell, thereby reducing toxicity (Ackerman et al., 2018; Listenberger et al., 2003).

Another proposed function of lipid droplet formation is to protect cells from lipid peroxidation. During oxidative stress, reactive oxygen species (ROS) attack lipids and generate toxic lipid peroxides and reactive aldehydes. Polyunsaturated fatty acids on membranes are especially vulnerable to peroxidation, and during oxidative stress, they are replaced on membranes and converted into triglycerides in lipid droplets. Failure to form lipid droplets results in increased lipid peroxidation on cellular membranes (Bailey et al., 2015). Exactly how lipid droplets

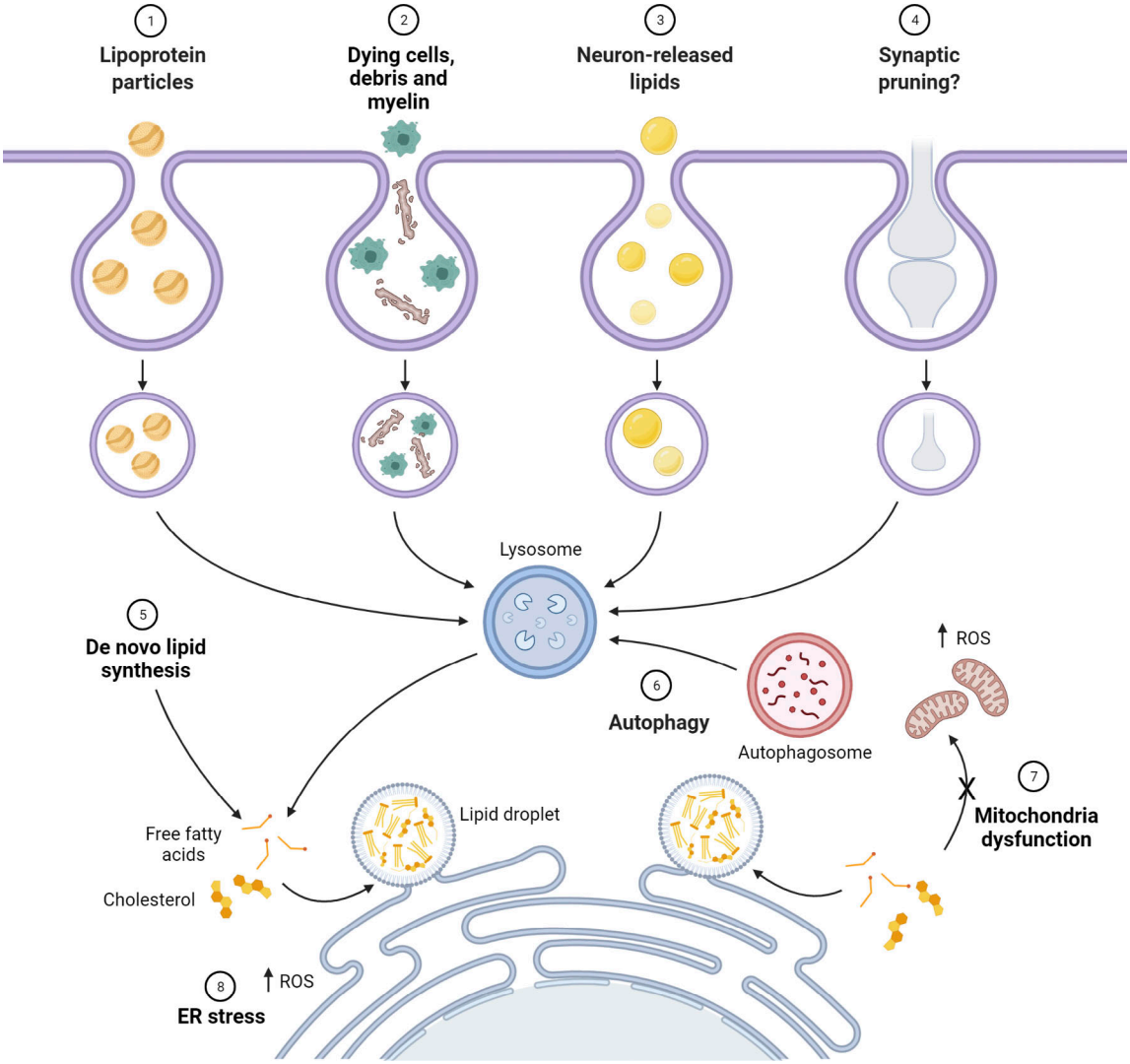

Figure 2. **Lipid droplet formation in the nervous system.** Schematic summarizing the known and hypothesized triggers of lipid droplet formation within cells in the nervous system. ROS, reactive oxygen species.

function to alleviate lipid peroxidation on membranes remains unclear, since they could act by sequestering peroxidated fatty acids to protect cellular membranes from ROS propagation (Liu et al., 2015), or they could serve to store unmodified polyunsaturated fatty acids to protect them from becoming peroxidated (Bailey et al., 2015). Failure to regulate lipid peroxidation can cause ferroptosis, a form of cell death caused by the iron-dependent accumulation of lipid peroxides (Dixon et al., 2012). Ferroptosis is functionally and biochemically distinct from lipoapoptosis, where fatty acids act as detergents and disrupt membrane integrity (Unger and Orci, 2002; Nguyen et al., 2017), although considerable crosstalk between the two pathways exists (Hong et al., 2017). Despite lipid droplets' known role in reducing lipid peroxidation and lipotoxicity (Nguyen et al., 2017; Bailey et al., 2015), addition of monounsaturated fatty acids can suppress ferroptosis even in the absence of lipid droplet formation (Magtanong et al., 2019). Perhaps lipid droplet protection from lipid-mediated toxicity becomes critical in the absence of exogenous fatty acids, during starvation for example. A better understanding of how lipid droplets sequester fatty acids during various forms of cell stress should help shed light on how they protect cells from lipid-mediated toxicity. This knowledge will have important implications in understanding how lipid droplets regulate the health of the brain, as ferroptosis has now been described in several neuropathologies (Bao et al., 2021; Magtanong and Dixon, 2018; Do Van et al., 2016). The various triggers associated with lipid droplet formation in the brain are summarized in Fig. 2.

Lipid droplet turnover

Two main mechanisms regulate lipid droplet turnover: lipolysis and lipophagy. During lipolysis, lipases bind the surface of lipid droplets and catalyze the sequential hydrolysis of triglycerides into free fatty acids and glycerol (Fig. 1 C). In most cells, the first and rate-limiting step of triglyceride hydrolysis is performed by adipose triglyceride lipase (ATGL; Zimmermann et al., 2004). While ATGL is present and functional in the brain, DDHD2 appears to be the primary brain triglyceride lipase (Yang et al.,

2020; Inloes et al., 2014). The second mechanism of lipid droplet turnover is lipid droplet–specific autophagy, or lipophagy (Fig. 1 D). Here, portions of lipid droplets are engulfed in autophagosomes, which fuse with lysosomes containing lysosomal acid hydrolase, which hydrolyzes triglycerides (Singh et al., 2009a; Schulze et al., 2017). Although lipophagy has been speculated to occur in the brain (Marschallinger et al., 2020), evidence of whether this process is commonly used in the brain is sparse. Moreover, it is still unclear how cells decide whether to use lipolysis or lipophagy to turn over lipid droplets. Nonetheless, there is considerable crosstalk between the two pathways (Cohen, 2018).

Lipid droplet regulatory proteins

The unique proteome of lipid droplets regulates their formation, maturation, and turnover (Bersuker et al., 2018; Krahmer et al., 2013). Proteins can be distributed to lipid droplets via two independent mechanisms (Kory et al., 2016). The first mechanism involves class I proteins that target lipid droplets from the ER. Class I proteins contain hydrophobic motifs that often adopt a hairpin topology and are embedded in the ER. During lipid droplet biogenesis, class I proteins diffuse from the ER to lipid droplets through the ER–lipid droplet continuum and then accumulate on lipid droplet membranes. For example, spastin is a class I protein and is involved in neurodegeneration (Park et al., 2010). Class II proteins contain an amphipathic helix or stretch of hydrophobic residues that target the lipid droplet surface from the cytoplasm. Class II proteins are often recruited to lipid droplets depending on their requirements for growth or cellular metabolism. Examples of class II proteins include perilipins (PLINs), important modulators of lipolysis (Krahmer et al., 2011; Čopič et al., 2018). PLINs regulate lipolysis by controlling access of the lipid droplet surface to various lipases and their cofactors. For example, PLIN1 prevents activation of ATGL, thereby preventing lipolysis of triglycerides (Yamaguchi et al., 2004). PLIN4 similarly enhances lipid droplet formation and is up-regulated in the brain of toxin-induced models of Parkinson's disease (Han et al., 2018).

Cell type specificity of lipid droplets in the brain

The lipid profiles of various cell types in the brain are remarkably different (Fitzner et al., 2020). Consistently, the relative abundance of lipid droplets within the different cells of the brain also differs. Below, we introduce the cell types that are found in the brain and describe the conditions under which they form lipid droplets (Table 1).

Neurons

Neurons have low triglyceride levels, and evidence that lipid droplets form in neurons in vivo is limited (Yang et al., 2020; Wat et al., 2020). This is likely because neurons are constantly turning over triglycerides to synthesize phospholipids for membrane production (Yang et al., 2020; Inloes et al., 2014). However, lipid droplets are frequently detected in cultured neurons from the hippocampus (Ioannou et al., 2019a), dorsal root ganglion (Yang et al., 2020), striatum (Martinez-Vicente et al., 2010), hypothalamus (Kaushik et al., 2011), and giant cerebral neuron of Aplysia (Savage et al., 1987). The number of neuronal lipid droplets is enhanced by cellular stress, such as excitotoxicity (Ioannou et al., 2019a), expression of mutant huntingtin (Martinez-Vicente et al., 2010), or treatment with fatty acids (Kaushik et al., 2011; Ioannou et al., 2019a). The enzymes regulating lipid droplet formation and turnover in neurons resemble those in other cell types: DGAT1 and phosphatidic acid phosphatase 1 promote triglyceride synthesis, while ATGL and DDHD2 actively hydrolyze triglycerides (Yang et al., 2020; Inloes et al., 2014). Unlike other cell types that store neutral lipids until they can be consumed for energy production, neurons have a limited capacity for fatty acid catabolism. This is due in part to the ROS generated by fatty acid catabolism, to which neurons are vulnerable because of their relatively poor antioxidant defenses compared with other cell types in the brain (Schönfeld and Reiser, 2013, 2017). Instead, fatty acids hydrolyzed from lipid droplets can be used to remodel and regenerate neurites (Yang et al., 2020). In addition, as is discussed below, fatty acids can be expelled and taken up by neighboring astrocytes and microglia.

Astrocytes

Astrocytes, the most abundant cell type in the central nervous system, help regulate a myriad of important brain functions, including neurogenesis, synapse formation, ion and water homeostasis, modulation of neurotransmitters, and providing direct metabolic and antioxidant support to neurons (Khakh and Sofroniew, 2015; Becerra-Calixto and Cardona-Gómez, 2017). Astrocytes are emerging as a prominent cell type that forms lipid droplets in response to cellular stress. Cultured astrocytes often form lipid droplets; however, this is likely influenced by the culture conditions used to grow them, as culturing cells from the brain can induce cell stress (Liddelow et al., 2017). Astrocytes that undergo morphological and functional changes in response to pathological stimuli are classified as reactive astrocytes (Escartin et al., 2021). Lipid droplets in astrocytes may indicate a reactive phenotype associated with neurotoxicity, as they have increased inflammatory markers (Kwon et al., 2017; Ioannou et al., 2019a). Astrocytes increase lipid droplet formation in response to hypoxia, metabolic stress (Smolič et al., 2021), and treatment with fatty acids (Nakajima et al., 2019; Kwon et al., 2017). The latter is observed in vivo during conditions that disrupt the blood–brain barrier. A leaky blood–brain barrier allows triglyceride-rich lipoprotein particles from the periphery to enter the brain and cause lipid droplet formation in astrocytes and up-regulation of several inflammatory-related genes (Lee et al., 2017). The role of developmental and neurodegenerative disease–associated lipid droplets in astrocytes is discussed in detail below. Once astrocytes form lipid droplets, they can catabolize fatty acids stored within these droplets. The genes needed to perform β-oxidation and oxidative phosphorylation are highly expressed by astrocytes (Eraso-Pichot et al., 2018; Hofmann et al., 2017). Astrocytes rely on β-oxidation of fatty acids stored in lipid droplets for survival during starvation (Cabodevilla et al., 2013).

Microglia

Microglia are the resident macrophages in the brain and, like macrophages, form lipid droplets during stress such as inflammation

Table 1. **Cell types in the brain with lipid droplets**

Setting	Cell type	Reference[a]
Development	Oligodendrocytes	Hayashi and Su, 2004
	Glia (*Drosophila*)	Bailey et al., 2015
	Astrocytes	Lucken-Ardjomande Häsler et al., 2014
Aging	Neurons	Shimabukuro et al., 2016
	Microglia	Shimabukuro et al., 2016
		Marschallinger et al., 2020
	Astrocytes	Shimabukuro et al., 2016
	Ependymal cells	Shimabukuro et al., 2016
Alzheimer's disease	Neurons	Yang et al., 2014
	Glia (*Drosophila*)	Liu et al., 2017
	Myeloid cells	Derk et al., 2018
	Ependymal cells	Hamilton et al., 2015
	Astrocytes	Qi et al., 2021
HSP	Neurons	Papadopoulos et al., 2015
		Renvoisé et al., 2016
	Astrocytes	Mou et al., 2020
Amyotrophic lateral sclerosis	Astrocytes	Chaves-Filho et al., 2019
		Jiménez-Riani et al., 2017
Parkinson's disease	Neurons	Brekk et al., 2020
		Cole et al., 2002
	Microglia	Brekk et al., 2020
Huntington's disease	Neurons	Martinez-Vicente et al., 2010
Multiple sclerosis	Neurons	Kim et al., 2015
	Microglia	Grajchen et al., 2018
Stroke	Astrocytes	Ioannou et al., 2019a
	Microglia	Gasparovic et al., 2001
		Ioannou et al., 2019a

[a]Relevant literature linking lipid droplets to distinct cell types in development, aging, or disease. Includes studies using in vitro and/or in vivo model systems.

and oxidative stress (Kaur and You, 2000; Marschallinger et al., 2020). Although the classification of reactive microglial subtypes is controversial, microglia display a wide range of phenotypes depending on the type of stimuli encountered (Ransohoff, 2016). For example, LPS treatment causes reactive microglia to undergo metabolic reprogramming including the reduction of oxidative mitochondrial metabolism (Chausse et al., 2019). The reduced capacity of LPS-treated microglia to oxidize fatty acids in mitochondria would likely lead to an accumulation of fatty acids stored in lipid droplets. Microglia also become reactive when treated with conditioned medium from lipid-loaded astrocytes (Kwon et al., 2017). There are several important sources of lipids for the formation of microglial lipid droplets, including the phagocytosis and/or endocytosis of dead cells (Krasemann et al., 2017), myelin debris (Cantuti-Castelvetri et al., 2018; Nugent et al., 2020), lipoprotein particles (Kunjathoor et al., 2004), and neuron-derived lipid particles (Ioannou et al., 2019a). Reduced phagocytic capacity of lipid droplet–containing microglia (Marschallinger et al., 2020) suggests a possible feedback system where excessive lipid droplet accumulation in these cells impedes rates of phagocytosis.

Oligodendrocytes

Oligodendrocytes ensure rapid electrical conduction of neurons by wrapping an insulating layer of myelin around axons during postnatal development. As 80% of myelin is made up of lipid, predominantly cholesterol, oligodendrocytes are a key cell type in regulating lipid homeostasis in the brain. While oligodendrocytes largely synthesize their own cholesterol for myelin production, they can also use cholesterol synthesized by neighboring cell types (Saher et al., 2005). Like other glial cells, oligodendrocytes can metabolize fatty acids (Hofmann et al., 2017). Lipid droplets appear in oligodendrocytes during periods involving myelination and/or demyelination. This includes during aging, when myelin is degraded and/or catabolized (Klosinski et al., 2015), and during development, when large

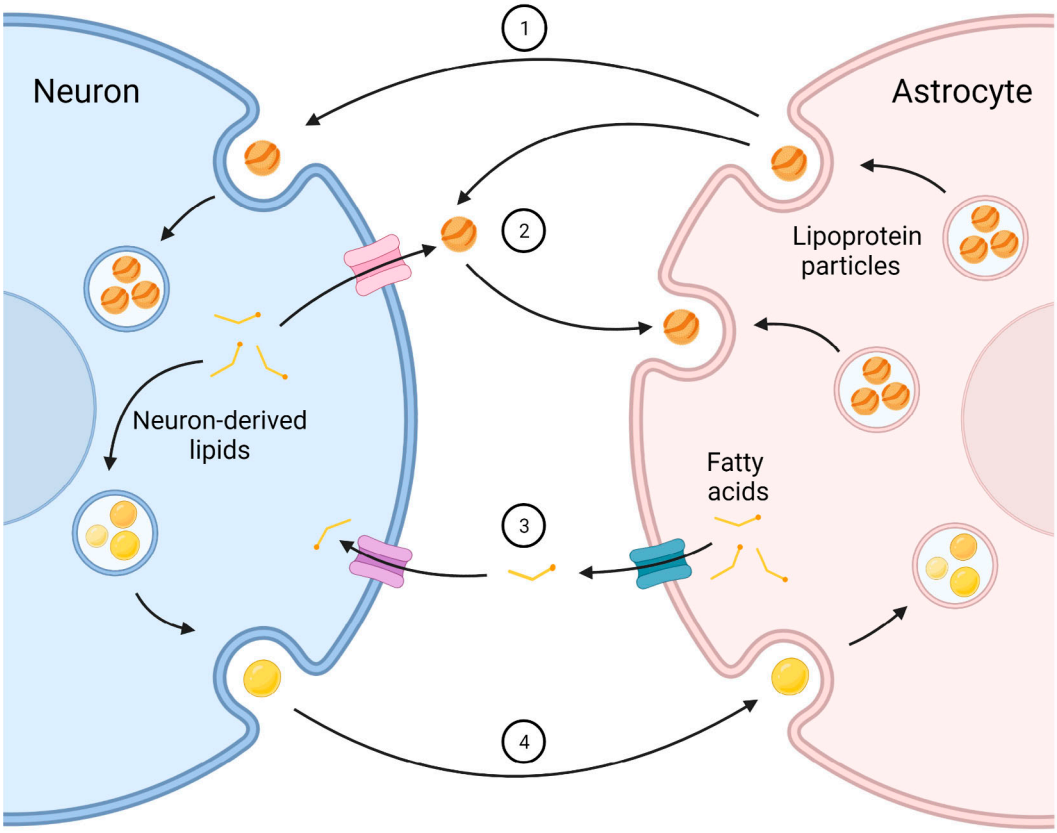

Figure 3. **Lipid transfer in the nervous system.** Schematic summarizing proposed pathways of lipid transfer between neurons and astrocytes. (1) Astrocytes secrete lipoprotein particles rich in cholesterol that are internalized by neurons (Lane-Donovan et al., 2014). (2) Lipoprotein particles are loaded with neuron-derived lipids through ABCA transporters. Lipoprotein particles are endocytosed by astrocytes (Moulton et al., 2021). (3) Fatty acids bound to albumin are transported from astrocytes to neurons during development (Tabernero et al., 2001). (4) Neuronal lipids are released, possibly as specialized lipid particles, and endocytosed by astrocytes (Ioannou et al., 2019a).

amounts of cholesterol are synthesized (Hayashi and Su, 2004). It has also been reported that lipid droplet numbers are higher in immature oligodendrocyte precursors compared with mature oligodendrocytes (Hayashi and Su, 2004). The mechanistic basis for why lipid droplet numbers vary in oligodendrocytes during development and under different conditions remains unknown.

Ependymal cells

Ependymal cells are highly polarized postmitotic glial cells that line the cerebral ventricles (Spassky et al., 2005). They act as a barrier between the brain parenchyma and the cerebrospinal fluid (CSF). Like neurons and astrocytes, ependymal cells are derived from radial glia early in development (Merkle et al., 2004; Mo et al., 2007; Spassky et al., 2005). Beating of their multiple cilia helps circulate CSF, thereby delivering nutrients and eliminating waste (Worthington and Cathcart, 1963; Olstad et al., 2019), creating a gradient of signaling molecules for neuronal migration (Sawamoto et al., 2006) and stem cell proliferation (Petrik et al., 2018) during development. A distinguishing feature of ependymal cells is the presence of lipid droplets. In fact, ependymal cells are the only cell types in the brain that form significant numbers of lipid droplets under nonpathological conditions, albeit at lower levels in young animals and increasing with age (Capilla-Gonzalez et al., 2014; Bouab et al., 2011). Internalization of CSF lipoprotein particles may contribute to lipid droplet formation in ependymal cells, as they express several lipoprotein receptors including CD36 and low-density lipoprotein receptors LRP1 and LRP2 (Matsumoto et al., 2015; Enos et al., 2019; Gajera et al., 2010). Consistently, in animals fed a high-fat diet, ependymal cells in the hypothalamus that regulate nutrient intake have more lipid droplets (Zhang et al., 2013; Rawish et al., 2020).

Lipid transport in the nervous system

Neurons and glia exhibit considerable crosstalk, which is important for maintaining the health and function of the nervous system. This includes the coupling of lipid metabolism between neurons and glia. Important for this coupling process is the transfer of various lipids between different cell types in the brain (Fig. 3).

Glia-to-neuron lipid transport

The transfer of lipids from astrocytes to neurons is a well-characterized process of which several detailed reviews have been written (Wang and Eckel, 2014; Mahley, 2016). In brief, while neurons produce cholesterol, they do not produce an adequate amount to support functions such as synapse formation, for which they require astrocyte-derived cholesterol (Mauch

et al., 2001). Cholesterol supplied by astrocytes also promotes axonal growth (Hayashi et al., 2004; Holtzman et al., 1995). Cholesterol and phospholipids produced by astrocytes are transferred to neurons bound to apolipoprotein E (ApoE)-containing lipoproteins (Mauch et al., 2001; Hayashi et al., 2004). ApoE is the major cholesterol carrier in the brain and is mainly expressed by astrocytes (Boyles et al., 1985). Internalization of cholesterol from ApoE-containing lipoproteins by neurons is mediated by the low-density lipoprotein receptor family (Beffert et al., 2004).

Lipids are also transported from astrocytes to neurons independently of lipoprotein particles. During development, astrocytes secrete oleic acid bound to albumin that is used by neurons to synthesize new membranes (Tabernero et al., 2001). Phosphatidic acid secreted from astrocytes influences the phospholipid composition of neuronal membranes and promotes neurite outgrowth (Zhu et al., 2016). Finally, soluble glycerophospholipids secreted from astrocytes regulate intracellular signaling in neurons during development (Guy et al., 2015). Altogether, these studies support an important role for lipids released from glia in neuronal physiology.

Neuron-to-glia lipid transport

More recently, the discovery that neurons transfer lipids to glial cells has gained significant attention. During oxidative stress, neurons generate excess free fatty acids. In the case of excitotoxicity, this is due to increased autophagy breaking down organelles damaged by ROS (Ioannou et al., 2019a). Increased ROS also activates sterol regulatory element binding protein, a transcription factor that drives de novo synthesis of fatty acids and cholesterol (Liu et al., 2015; Horton et al., 2002). Since excess fatty acids can cause lipotoxicity, or become peroxidated by ROS leading to ferroptosis, excess lipids need to be removed from the cytosol. Non-neuronal cells are protected by storing extra lipids generated during cellular stress in lipid droplets. However, neurons form a minimal number of lipid droplets and have a limited capacity for fatty acid catabolism (Schönfeld and Reiser, 2013, 2017). Additionally, oxidative stress induces mitochondrial fragmentation and dysfunction (Jahani-Asl et al., 2007; Barsoum et al., 2006). Fragmented mitochondria are inefficient at catabolizing fatty acids and susceptible to autophagic degradation (Rambold et al., 2015, 2011). Instead, neurons transfer fatty acids to neighboring glial cells to be stored in glial lipid droplets (Liu et al., 2015, 2017; Ioannou et al., 2019a,b; Qi et al., 2021). By taking up neuron-derived lipids, glia can protect neurons from lipid-mediated toxicity.

While the mechanisms of this lipid transfer are still poorly understood, there is a clear role for ApoE in the process. Knockdown of ApoE in either neurons or glia reduces the transfer of lipids from neurons to glia and subsequent glial lipid droplet formation (Liu et al., 2017; Ioannou et al., 2019a). But how ApoE regulates this transfer is unknown. Neuronal transporters (ABCA1 and ABCA7) that package neuronal lipids, presumably into astrocyte-derived lipoprotein particles, contribute to glial lipid droplet formation (Moulton et al., 2021 *Preprint*). Astrocytic ApoE likely regulates lipid transport from neurons to glia while associated with these lipoprotein particles. ApoE secreted from neurons also contributes to lipid transfer (Liu et al., 2017; Ioannou et al., 2019a). Because neurons express ApoE only during oxidative stress (Boschert et al., 1999; Xu et al., 2006), this suggests that they may up-regulate ApoE to facilitate this lipid transfer. It is possible that neuronal ApoE is released unbound to lipid and also associates with astrocyte-derived lipoprotein particles. However, ApoE colocalizes with neutral lipids in cultured neurons, and adult neurons in vivo contain lipid particles enclosed in vesicles (Ioannou et al., 2019a), suggesting that neurons may directly release specialized lipid particles. This raises another important question: What type of lipids are being transferred? Do neurons release free fatty acids, neutral lipids, or perhaps both? While the abundance of neutral lipids in the brain is kept very low, neurons are constantly turning over triglycerides to synthesize phospholipids for generating and remodeling membranes (Inloes et al., 2014; Yang et al., 2020). Perhaps this pathway may be diverted to generate more neutral lipids during periods of stress. More work is needed to better understand the multiple mechanisms that neurons use to rid themselves of excess lipids during cellular stress.

Lipid droplets in the healthy brain

Development

The composition of lipids in tissues varies and depends on the developmental stage of the organism. The brain is enriched in sterols and phospholipids and contains neutral lipids composed of longer and more polyunsaturated fatty acids than other tissues (Carvalho et al., 2012). Given the presence of neutral lipids in the *Drosophila* brain (Carvalho et al., 2012), it is not surprising that lipid droplets would also be present. In developing *Drosophila* larva, lipid droplets form in glial cells, with accumulation being most extensive in cortex glial cells that insulate neuroblast cell bodies near the surface of the brain (Kis et al., 2015; Bailey et al., 2015). That said, it remains unclear whether and how lipid droplets affect the lipid composition and metabolism in these cells during development (Welte, 2015).

Lipid droplets are, however, important for protecting neuronal stem cells from oxidative stress during development. Neuroblasts are neural stem cells that give rise to multiple cell types in the brain, including neurons and glia. They reside in a largely hypoxic stem cell niche, and their proliferative capacity is enhanced by hypoxic conditions (Morrison et al., 2000; Mohyeldin et al., 2010). Hypoxia increases lipid droplet formation in the developing *Drosophila* brain (Bailey et al., 2015). Inhibiting lipid droplet formation in cortex glial cells increases oxidative stress, including lipid peroxidation in neuroblasts, and decreases their proliferative capacity (Bailey et al., 2015). Through their antioxidant function, glial lipid droplets protect neuroblasts from the oxidative stress associated with hypoxia and directly influence their ability to proliferate.

Another potential function for lipid droplets in the developing brain is through the regulation of histones. *Drosophila* embryos sequester extranuclear histones on the surface of lipid droplets and release them during periods of high chromatin assembly (Li et al., 2012; Stephenson et al., 2020 *Preprint*). Stockpiling histones on lipid droplets is critical during *Drosophila*

embryogenesis, where the demand for histones often exceeds the ability to synthesize them (Johnson et al., 2018). Since histone availability affects neural stem cell self-renewal and neurogenesis (Wang et al., 2018), lipid droplets may similarly buffer histone levels in neural stem cells to control transcription during development. Moreover, excess histones are toxic (Singh et al., 2009b). Sequestering histones on lipid droplets may similarly protect neural stem cells from the toxicity associated with histones, as they do during *Drosophila* embryogenesis (Johnson et al., 2018).

Few studies have looked at lipid droplets in the developing mammalian brain. GFAF1a is a brain-specific protein that promotes lipid droplet growth by inhibiting lipolysis. GRAF1a expression in mice increases progressively in postnatal glial cultures (predominantly astrocytes) but is largely absent from the adult brain (Lucken-Ardjomande Häsler et al., 2014). The time course of GRAF1a expression in the mouse brain coincides with periods of astrogenesis, synaptic pruning, and programmed neuronal death (Reemst et al., 2016; Morimoto and Nakajima, 2019). One possibility is that glial lipid droplets form in response to the influx of membranes that result from phagocytosis of synapses and clearance of cell debris. However, lipid droplets have yet to be shown in developing mouse brains in vivo, so it remains unclear what role they may play in the developing brain in mammals.

Aging

Since aging is an inevitable part of life, including in healthy individuals, we discuss aging under the category of lipid droplets in the healthy brain. Various changes take place inside the aging brain. Structurally, this includes degeneration of myelin (Wang et al., 2020) and a loss in total brain volume (Farokhian et al., 2017). Cellularly, microglia and astrocytes become activated and reactive (Capilla-Gonzalez et al., 2014), neuronal synapses are altered as dendritic branching and spine density decreases (Kabaso et al., 2009), and ependymal cells lose their cilia (Capilla-Gonzalez et al., 2014). These alterations, from the loss of membrane-containing compartments to the activation of glial cells, are all associated with lipid droplet formation. Not surprisingly, lipid droplet accumulation in aged brains has been reported in several studies.

Lipid droplets are found in microglia, astrocytes, neurons, and ependymal cells within multiple regions of the aged brain (Shimabukuro et al., 2016). Lipid droplets colocalize with the autophagy marker LC3, which may indicate that lipophagy is used to degrade lipid droplets in the brain (Shimabukuro et al., 2016). Chaperone-mediated autophagy decreases with age (Cuervo and Dice, 2000; Madeo et al., 2010). If lipophagy also decreases with age, this could contribute to the lipid droplet accumulation observed with age.

Lipid droplets are most abundant in microglia in the aged brain (Marschallinger et al., 2020). Microglia become increasingly dysfunctional with age as their protective capacity is diminished. They exhibit increased levels of oxidative stress, decreased phagocytosis, and increased proinflammatory signaling (Mosher and Wyss-Coray, 2014). These alterations are exacerbated in microglia containing lipid droplets (Marschallinger et al., 2020). For example, the proinflammatory endotoxin LPS increases phagocytosis in microglia without lipid droplets, but this effect is lost in those containing lipid droplets (Marschallinger et al., 2020). During aging, microglia consume excess lipids during aberrant clearance of synapses, myelin, and cell debris (Safaiyan et al., 2016; Tremblay et al., 2012). Their ability to internalize lipid-rich materials would be enhanced from proinflammatory signals (Raj et al., 2017; Zhang et al., 2013). Finally, microglia appear to reach a threshold as they become overwhelmed with lipids, which triggers genetic reprogramming as they lose their protective function in the brain (Marschallinger et al., 2020).

Lipid droplets in the diseased brain

Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disease. The most notable symptom of Alzheimer's disease is memory loss due to loss of hippocampal neurons early in the disease before spreading to other cortical and subcortical areas. Alzheimer's disease is characterized primarily by extracellular plaques composed of aggregated amyloid-β and intracellular tangles composed of hyperphosphorylated tau (Long and Holtzman, 2019). When Alois Alzheimer first characterized Alzheimer's disease in 1907, in addition to plaques and tangles, he also noted that many glial cells contained "adipose saccules" or lipid droplets (Alzheimer [1907]; translated in Stelzmann et al. [1995]). Yet despite knowing that lipid droplets appear in the disease, it took more than a century for scientists to start focusing their attention on them. The formation of lipid droplets in models of Alzheimer's disease with different genetic backgrounds highlights their involvement as a converging mechanism for the disease. Lipid droplet accumulation in Alzheimer's mouse models precedes the formation of amyloid plaques and neurofibrillary tangles (Hamilton et al., 2015). This underscores the importance of dysregulation of lipids in driving Alzheimer's pathology.

Lipid droplets accumulate in ependymal cells of triple-transgenic Alzheimer's disease mice and postmortem Alzheimer's diseased brains (Hamilton et al., 2015). In transgenic models of Alzheimer's disease, increased lipid droplets in ependymal cells suppress neural stem cell proliferation (Hamilton et al., 2015). These results are at odds with early development studies showing that lipid droplet formation promotes neural stem cell proliferation (Bailey et al., 2015). The physiology and consequences of lipid droplet formation on stem cell proliferation in development versus neurodegeneration needs to be further explored.

One important mechanism of glial lipid droplet formation in Alzheimer's disease is from toxic lipids derived from neurons (Liu et al., 2017; Moulton et al., 2021 *Preprint*). This lipid transport depends on ApoE, encoded by a polymorphic gene that is the most common genetic risk factor for late-onset Alzheimer's disease. The ApoE4 allele has the highest risk for developing the disease (Corder et al., 1993; Strittmatter et al., 1993), while the E2 and E3 alleles are neuroprotective (Corder et al., 1994). ApoE isoforms differ in their lipid-binding capacity and protein stability (Liu et al., 2013). ApoE4 is degraded more rapidly (Riddell et al., 2008), has decreased affinity for brain-specific lipoprotein

particles (Dong and Weisgraber, 1996), and in its nonlipidated form, binds ApoE receptors less efficiently (Frieden et al., 2017). In *Drosophila*, knockdown of the apolipoprotein lazarillo abolished glial lipid droplet formation during oxidative stress and could be rescued with human ApoE3 but not ApoE4 (Liu et al., 2017). Similarly, knockdown of ApoE or expression of ApoE4 reduces lipid transfer from neurons to glia in mammalian cells (Liu et al., 2017; Ioannou et al., 2019b; Qi et al., 2021). Interestingly, ApoE knockdown in either neurons or glia alone can reduce lipid transport to glia in vitro and reduces lipid droplet formation in vivo (Liu et al., 2017; Ioannou et al., 2019a; Qi et al., 2021). Since neurons express ApoE only during oxidative stress, they likely up-regulate the protein to facilitate this lipid transfer (Ioannou et al., 2019a; Sun et al., 1998). The mechanisms of ApoE derived from different cell types in this lipid transport are still unclear. Astrocyte-derived ApoE likely mediates transport while associated with lipoprotein particles that are loaded with neuronal lipids and endocytosed by astrocytes. Several Alzheimer's disease risk genes are consistent with this mechanism of lipid transport, including lipid transporters *ABCA1* and *ABCA7* in neurons, ApoE receptor *LRP1* in glia, and several endocytic genes including *PICALM*, *CD2AP*, and *AP2A2* in glia (Moulton et al., 2021 *Preprint*). Neuronal-derived ApoE may associate with these lipoprotein particles, or it may function independently by mechanisms that are yet to be determined.

Given its role in lipid transport, it is not surprising that ApoE affects the number of lipid droplets within a cell. In the absence of neurons, ApoE4-expressing glia accumulate more lipid droplets (Qi et al., 2021; Farmer et al., 2019). These opposing effects on lipid droplets could be explained by the bidirectional nature of lipid transport in the brain. In the absence of functional ApoE, transport of lipoprotein-like particles from astrocytes to neurons is reduced, resulting in neutral lipids stockpiling within astrocytes. At the same time, stressed neurons become less efficient at transporting excess toxic lipids to astrocytes during periods of oxidative stress. In either case, glial lipid droplets are neuroprotective, as failure to form them results in more severe neurodegeneration (Liu et al., 2015, 2017). In addition to regulating lipid transport between cells, the direct and/or indirect regulation of lipid metabolism and membrane trafficking by ApoE likely plays additional roles in mediating lipid droplets in the cell (Nuriel et al., 2017; Narayan et al., 2020; Lin et al., 2018).

Hereditary spastic paraplegia (HSP)

HSP is a group of inherited neurological disorders with a prominent feature of lower-extremity spasticity, primarily due to the degeneration of corticospinal nerves (Blackstone, 2018). Several HSP-associated proteins promote lipid droplet growth, including ER-resident proteins atlastin-1 (Klemm et al., 2013), REEP1 (Renvoisé et al., 2016; Falk et al., 2014), and seipin (Salo et al., 2019, 2016). Seipin localizes to the ER–lipid droplet interface to facilitate triglyceride flow from the ER to lipid droplets during their biogenesis (Salo et al., 2019, 2016; Fei et al., 2008). Atlastin-1 and REEP1 form a complex with another HSP-associated protein, spastin (Park et al., 2010). Spastin resides on lipid droplets and regulates the subcellular distribution of lipid droplets through its microtubule-severing activity (Papadopoulos et al., 2015). By severing microtubules and decreasing lipid droplet dispersion, spastin promotes triglyceride formation and lipid droplet growth (Papadopoulos et al., 2015; Arribat et al., 2020). Spastin can also promote lipid droplet contacts with peroxisomes to facilitate fatty acid trafficking into peroxisomes (Chang et al., 2019). This underlies the role of spastin in reducing cellular levels of lipid peroxidation (Chang et al., 2019). Another HSP-associated protein, DDHD2, functions as a triglyceride lipase on the surface of lipid droplets to release fatty acids (Inloes et al., 2014, 2018). Finally, the HSP-associated protein spartin controls lipid droplet turnover, although the mechanism remains unknown (Eastman et al., 2009). These studies all point to disruption of fatty acid flux from lipid droplets as an underlying feature in the pathogenesis of HSP.

The relevance of lipid droplet regulation to motor neuron health remains unknown. While lipid droplets have been reported in neurons, they are rare, even in diseased states (Pennetta and Welte, 2018). Since neuronal lipid droplets may be transient and/or difficult to detect, it is unclear if defects in lipid droplet homeostasis within motor neurons are a major driver of disease. Mutation of HSP proteins may also result in disease pathogenesis in other cell types in the brain. A related motor neuron disease, amyotrophic lateral sclerosis, has lipid droplet accumulation in glial cells surrounding motor neurons (Chaves-Filho et al., 2019; Jiménez-Riani et al., 2017). This is similar to other neurodegenerative diseases described above (Liu et al., 2017, 2015; Ioannou et al., 2019a). The ability of glial cells to protect neurons by internalizing toxic lipids released by neurons may be a common feature of neurodegeneration that includes motor neuron disease. Further studies are required to understand how these HSP-associated proteins regulate lipid droplet turnover and how this contributes to motor neuron degeneration.

Parkinson's disease

Parkinson's disease, the second most common neurodegenerative disease, involves motor symptoms such as tremors, rigidity, and bradykinesia and non-motor symptoms such as sleep disturbances and cognitive impairment (Poewe et al., 2017). It is predominantly characterized by the loss of dopaminergic neurons in the substantia nigra and intracellular aggregation of α-synuclein protein (Poewe et al., 2017; Panicker et al., 2021). Disturbances in lipid homeostasis have recently emerged as a common theme in Parkinson's disease. New genetic studies increasingly point to lipid-associated pathways, and lipid-targeting drugs show great potential for improving toxicity in Parkinson's disease (Fanning et al., 2021; Vincent et al., 2018). In fact, Parkinson's disease is now being suggested as a lipidopathy, a disease caused by lipid dysfunction (Fanning et al., 2020). For example, α-synuclein interacts with phospholipid membranes under physiological conditions, and the composition of those membranes affects its propensity to aggregate (Ysselstein et al., 2015; O'Leary et al., 2018). One membrane that α-synuclein associates with is the phospholipid monolayer on the surface of lipid droplets. By binding the surface, α-synuclein protects lipid droplets from lipolysis and promotes their accumulation (Cole et al., 2002; Outeiro and Lindquist, 2003). As in other neurodegenerative diseases, lipid droplets play a protective role, because preventing lipid droplet formation exacerbates

α-synuclein toxicity (Fanning et al., 2019). While total neutral lipid levels in the Parkinson's brain are unchanged, neutral lipids are increased in dopaminergic neurons and microglia and decreased in adjacent astrocytes (Brekk et al., 2020). This points to possible defects in neuron-to-astrocyte lipid transport in Parkinson's pathology, as is suggested for Alzheimer's disease and stroke (Liu et al., 2017; Moulton et al., 2021 *Preprint*; Ioannou et al., 2019a).

Huntington's disease

Huntington's disease is a neurodegenerative disease characterized by motor and cognitive deficits. It is caused by a dominant trinucleotide repeat expansion in the huntingtin gene, resulting in an abnormal polyglutamine expansion in the huntingtin protein (Bates et al., 2015). The length of the polyglutamine expansion is variable and correlates with disease severity. While huntingtin protein is ubiquitously expressed, neurons in the striatum are particularly susceptible to mutant huntingtin. Increased lipid droplets are present in cultured striatal neurons expressing mutant huntingtin, *Drosophila* cells expressing mutant huntingtin, and Huntington disease patient tissue (Martinez-Vicente et al., 2010; Aditi et al., 2016). This increase is caused, at least in part, by defects in macroautophagy (Martinez-Vicente et al., 2010). Whether lipid droplets form in striatal neurons in vivo, and the consequences of lipid droplet formation on neuronal health in Huntington's disease, remains to be elucidated.

Multiple sclerosis

Multiple sclerosis is a chronic neuroinflammatory and neurodegenerative disease involving demyelination of axons and subsequent degeneration of neurons in the central nervous system. Given that myelin is composed of 80% lipid, it is not surprising that lipid droplets are abundant in lesions where active demyelination occurs (O'Brien and Sampson, 1965; Grajchen et al., 2018). Lipid droplets are found predominantly in microglia and infiltrating macrophages during demyelination, when there is a pronounced increase in the phagocytic capacity of these cells (Voss et al., 2012). This likely results in lipid droplet formation as microglia consume myelin debris from the lesion. The ability of microglia to clear debris and apoptotic cells by phagocytosis is also required for remyelination to occur (Neumann et al., 2009). However, the phagocytic capacity of microglia during remyelination is compromised and contributes to disease progression (Voss et al., 2012). In this regard, microglia resemble those in the aging brain, where accumulation of lipid droplets coincides with increased oxidative stress, decreased phagocytosis, and increased proinflammatory signaling (Mosher and Wyss-Coray, 2014). The effects of lipid droplets on microglial physiology and subsequent remyelination are thus ripe areas for future research.

Stroke

The most prevalent form of stroke, ischemia, is caused by a disruption of blood flow and oxygen to the brain. Glutamate-induced excitotoxicity is the primary cause of cell death during ischemic stroke (Lai et al., 2014; Belov Kirdajova et al., 2020; Camacho and Massieu, 2006). Shortly after neurons are deprived of glucose and oxygen, their ATP stores are depleted. In the absence of ATP, ion pumps can no longer maintain electrochemical gradients, resulting in an influx of sodium and calcium ions, triggering release of the excitatory neurotransmitter glutamate. In healthy tissue, glial cells regulate extracellular glutamate levels and prevent excitotoxicity (Rothstein et al., 1996). During ischemia, however, glial transporters that remove excess glutamate from the extracellular space no longer function adequately (Camacho and Massieu, 2006). This further increases the amount of extracellular glutamate and the propagation of aberrant neuronal activation (Benveniste et al., 1984).

The causes of cell death during excitotoxicity following stroke include calcium overload, increased production of ROS, mitochondrial dysfunction, ER stress, and ferroptosis (Aarts et al., 2003; Xiong et al., 2004; Yoshida et al., 1982; Owens et al., 2015; Nakka et al., 2010). Most of these cellular insults can induce lipid droplet formation, and indeed, lipid droplets form in the brain following ischemic stroke. This was first shown in the middle cerebral artery occlusion model of ischemic stroke in rats using proton magnetic resonance spectroscopy (Gasparovic et al., 2001). Those authors used biochemical methods to show that neutral lipid signals arise from triglycerides and cholesteryl esters, the main components of lipid droplets. Lipid droplets also form in the brain following pial strip lesion models of stroke in rats (Ioannou et al., 2019a). Lipid droplets were largely found in the ischemic penumbra directly adjacent to the ischemic core. The infarct core is the area of severe ischemia where irreversible cell death occurs within hours of injury, while the penumbra is the area surrounding the infarct core where cell death occurs over several days (Carmichael, 2005).

Similar to other pathologies, lipid droplets formed during stroke are found predominantly in microglia as well as astrocytes (Gasparovic et al., 2001; Ioannou et al., 2019a). Several mechanisms may contribute to lipid droplet formation during stroke. One contributor could be the massive cell death occurring in a relatively short amount of time, which could lead to phagocytosis of dead cells by glial cells and subsequent lipid droplet formation. Another potential mechanism of lipid droplet formation during stroke could be an influx of peripheral lipoprotein particles caused by disruption of the blood–brain barrier (Doll et al., 2015; Jackman et al., 2013). Other factors, such as lipid transfer and direct exposure of glial cells to oxidative stress and nutrient deprivation, are also likely at play.

Glioma

Although lipid droplets were described in cancerous cells >50 yr ago, they have only recently gained significant attention from the research community (Tirinato et al., 2017; Ramos and Taylor, 1974). This includes the most common and lethal form of cancer in the brain, glioblastoma (Taïb et al., 2019). While undetectable in low-grade gliomas, lipid droplet formation correlates with progression to advanced-stage glioblastomas (Geng et al., 2016; Kohe et al., 2017). This is caused by an up-regulation of DGAT1 by glioblastomas, leading to increased production of neutral lipids (Cheng et al., 2020). Preventing lipid droplet formation using DGAT1 inhibitors increases the lipotoxicity of glioblastomas

and suppresses tumor growth in vivo in mouse models of glioblastoma (Cheng et al., 2020). Targeting lipid droplets offers a promising therapeutic approach for treating glioblastomas.

Infection

Lipid droplets play a fundamental role in the host–pathogen relationship, as evidenced by the rapid increase in lipid droplet numbers following infection with virus (Samsa et al., 2009; Monson et al., 2021), bacteria (D'Avila et al., 2006; Kumar et al., 2006), fungi (Sorgi et al., 2009), and protozoa (Vallochi et al., 2018; Melo et al., 2003; D'Avila et al., 2011; Rodríguez et al., 2017). The life cycle of many viruses is intimately tied to the host's lipid metabolism (Thomssen et al., 1992; Herker and Ott, 2012). Once inside the cell, lipid droplets serve as a platform for the assembly of the hepatitis C virus (Miyanari et al., 2007; Samsa et al., 2009). Hepatitis C is also released in association with lipoprotein particles (Thomssen et al., 1992). Similarly, efficient replication of the bacterium *Chlamydia trachomatis* requires lipid droplets (Kumar et al., 2006; Saka et al., 2015). Paradoxically, lipid droplets have recently been shown to actively participate in the immune response to pathogens by recruiting immune proteins to destroy the pathogen while reprogramming the cell metabolism to favor survival (Bosch et al., 2020).

Several pathogens that are reliant on lipid droplets can infect cells in the brain. Yet, little is known regarding the importance of lipid droplets during brain infections. For example, *Toxoplasma gondii*, a neurotropic parasite, is found primarily in neurons, likely owing to the inability of neurons to clear the pathogen (Cabral et al., 2016). *T. gondii* is often dormant in neurons and can be reactivated following infections such as HIV (Luft and Remington, 1992). Since *T. gondii* exploits lipid droplets to replicate (Nolan et al., 2017), it is possible that by inducing lipid droplet formation, HIV provides *T. gondii* with conditions that favor reactivation (Castellano et al., 2019). Another well-characterized inducer of lipid droplet formation is LPS, a glycolipid found on the outer membrane of Gram-negative bacteria. LPS binding to TLR4, CD14, and CD11b triggers lipid droplet formation (Pacheco et al., 2002). Cultured microglia form lipid droplets in response to LPS (Khatchadourian et al., 2012; Tremblay et al., 2016), and ependymal cells are highly susceptible to viral infection (Del Bigio, 2010), making both cell types likely to form lipid droplets during brain infections. Whether other cell types form lipid droplets following exposure to pathogens and whether lipid droplets form in vivo following infection remains to be determined.

Conclusions

Lipid droplets are emerging as an important organelle in the nervous system and are present in all cell types in the brain under different circumstances. Lipid droplet formation appears to have profound consequences on cellular health during disease progression in the brain. Yet, despite the abundance of lipid droplets in various neuropathologies, they have only recently been appreciated for the active role they play in regulating cellular stress in the brain. Since this field is relatively young, much remains to be discovered regarding the function of lipid droplets in the brain. The text box outlines a few of the many outstanding questions in the field. There will no doubt be great strides in our understanding of lipid droplets in the brain in the years to come.

Outstanding questions

What is the lipid and protein composition of lipid droplets in the brain, and how do they differ in different cell types and/or neuropathologies?

What are the mechanisms of glia-to-neuron and neuron-to-glia lipid transfer? Does the reliance on different mechanisms shift under different conditions?

What are the physiological consequences of accumulating lipid droplets? While glial lipid droplets serve a neuroprotective role, at what point do lipid droplets in glial cells cause toxicity and contribute to disease progression?

If defects in lipid droplet formation cause neurodegeneration, can they be targeted for improving outcomes in neuropathologies?

Can lipid droplets be used to detect and diagnose diseases in the brain? Examples include noninvasive imaging of neutral lipids using magnetic resonance spectroscopy or biochemical screening of patient-derived cells for lipid droplet formation.

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