HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2017 May 26.

Published in final edited form as:

Neuroscience. 2016 May 26; 323: 195–206. doi:10.1016/j.neuroscience.2015.05.061.

Astrocytes and Lysosomal Storage Diseases

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Abstract

Lysosomal storage diseases (LSDs) encompass a wide range of disorders characterized by inborn errors of lysosomal function. The majority of LSDs result from genetic defects in lysosomal enzymes, although some arise from mutations in lysosomal proteins that lack known enzymatic activity. Neuropathological abnormalities are a feature of several LSDs and when severe, represent an important determinant in disease outcome. Glial dysfunction, particularly in astrocytes, is also observed in numerous LSDs and has been suggested to impact neurodegeneration. This review will discuss the potential role of astrocytes in LSDs and highlight the possibility of targeting glia as a beneficial strategy to counteract the neuropathology associated with LSDs.

Keywords

Astrocytes; lysosomal storage diseases; mitochondrial dysfunction; neurodegeneration; reactive astrocytosis

INTRODUCTION

Lysosomes are essential organelles of eukaryotic cells whose function is degradation and recycling of macromolecules that are channeled through endocytosis, phagocytosis, and autophagy (Kroemer and Jaattela, 2005). Defects in lysosomal function may curtail degradation, which can result in the accumulation of substances within the lysosome. Lysosomal storage diseases (LSDs) represent a subgroup of inborn errors of metabolism primarily resulting from a deficiency of one or more lysosomal enzymes involved in macromolecule degradation, (for review see (Schultz et al., 2011, Cox and Cachon-Gonzalez, 2012, Platt et al., 2012, Boustany, 2013), although in some LSDs, the function of mutated protein(s) has yet to be determined (Bruun et al., 1991, Rakheja et al., 2007). Since the discovery of lysosomes by Christian de Duve (De Duve, 1963, 1966), over 60 distinct LSDs have been described, with a collective incidence estimated at 1:5,000 live births world-wide (Fuller et al., 2006). Roughly two thirds to three quarters of LSDs are neuropathic, which can affect multiple brain regions depending on the disease type. A few examples of LSDs that are associated with CNS pathology include, Gaucher disease, Krabbe disease, Sandhoff disease, Niemann-Pick Type C, and the group of neuronal ceroid lipofuscinoses (commonly referred to as Batten Disease; (Prada and Grabowski, 2013). This

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review will highlight select LSDs that affect the CNS, the neuropathological events associated with these disorders, and potential roles of reactive astrocytes in disease progression. The various enzymes/proteins that are mutated in the LSDs discussed in this review are all expressed in astrocytes, since they play a critical role in lysosomal homeostasis/function. However, an intriguing finding is that not all LSDs have dramatic CNS pathology, which brings into question the functional importance of mutated genes in the brain compared to other organs, even though all nucleated cells contain lysosomes. Even within the CNS, neuronal loss/dysfunction in many LSDs is often restricted to specific brain regions, which remains another enigma, since typically the mutated gene is ubiquitously expressed, although it is possible that differences in expression levels may dictate susceptibility. Another variable to consider is the cell type-specific impact of the mutation in neurons, astrocytes, microglia, or other populations, such as endothelial cells and how this influences pathology via autonomous or non-autonomous pathways. Alternatively, regional changes in the expression of other molecules that normally associate with the affected protein may be differentially regulated and could conceivably influence neuronal susceptibility in LSDs.

LSDs associated with enzyme deficiencies

Gaucher disease

Gaucher disease is caused by a deficiency in glucocerebrosidase (GBA), a lysosomal enzyme responsible for the degradation of glucocerebroside, an intermediate in glycolipid metabolism (Kampine et al., 1967, Jmoudiak and Futerman, 2005). Nearly 300 GBA mutations have been identified, including missense, nonsense, and frameshift mutations in addition to deletions, insertions, and complex alleles. Collectively, these mutations have been linked to 3 forms of Gaucher disease, classified as Type 1–3 (Grabowski et al., 1985). Type 1, also referred to as non-neuronopathic or adult Gaucher disease, is generally late onset and represents the most common form, with an ethnic predilection among Ashkenazi Jews (Gan-Or et al., 2008). Type 2 has the earliest onset, typically by 3 to 6 months of age, with death usually occurring by 2 years. Type 3 is a juvenile disease with an onset in early childhood. As a result of GBA deficiency, lysosomes accumulate several glycolipids, including glucocerebroside and glucosylsphingosine (Conradi et al., 1984, Farfel-Becker et al., 2014). The major cell type affected in Gaucher disease is the macrophage, where resident macrophage populations in the spleen and liver have perturbed homeostatic functions (Conradi et al., 1988). As a result, there is a marked splenomegaly, which destroys hematopoietic cells leading to anemia (Mandlebaum, 1912, Appel and Markowitz, 1971).

In terms of the CNS, the neuronopathic form of Gaucher disease has been associated with neurodegeneration in layer V of the cerebral cortex, lateral globus pallidus, various thalamic nuclei, and hippocampal CA2-CA4 regions (Conradi et al., 1984, Wong et al., 2004, Farfel-Becker et al., 2014). It is currently not well understood why these particular brain regions are selectively targeted given the ubiquitous expression of GBA; however, the collective evidence clearly indicates that it is not due to storage material accumulation (Vitner et al., 2012, Farfel-Becker et al., 2014, Vitner et al., 2014). The neuronopathic forms of Gaucher disease are also characterized by microglial proliferation, astrocytosis, and a robust

neuroinflammatory response (Vitner et al., 2012, Vitner and Futerman, 2013). A mouse model of Gaucher disease where GBA was selectively deleted in neurons and glial cells resulted in increased expression of the lysosomal enzyme cathepsin D in reactive astrocytes (Vitner et al., 2010a), which may represent a compensatory mechanism to offset GBA deficiency. However, the consequences of exaggerated cathepsin D expression in this model and the overall functional role that astrocytes play in Gaucher disease still remains to be identified. Interestingly, although the disease is known to target macrophage functions in the periphery, little information is available regarding the impact of GBA deficiency in microglia, although it has been shown that wild type microglia cannot rescue neurodegeneration associated with Gaucher disease (Enquist et al., 2007).

Krabbe disease

Krabbe disease, also known as globoid cell leukodystrophy (GLD), results from β-galactocerebrosidase deficiency, which catalyzes the hydrolysis of galactose from several sphingolipids, including galactosylceramide, lactosylceramide, and galactosylsphingosine, to generate ceramide and sphingosine (Andrews and Cancilla, 1970, Andrews et al., 1971). β-galactocerebrosidase loss leads to the accumulation of the toxic glycosphingolipid psychosine (Suzuki and Suzuki, 1985). Krabbe disease is an early onset LSD, with symptoms typically presenting around 6 months of age and mortality occurring by 2 years (Wenger et al., 1997). Krabbe disease primarily affects the CNS, resulting in extensive demyelination of cerebral white matter tracts leading to spasticity, ataxia, blindness, seizures, and severe dementia (Husain et al., 2004, Kohlschutter, 2013). The neuropathology associated with Krabbe disease has been attributed, in large part, to the abnormal accumulation of psychosine in the brain (Igisu and Suzuki, 1984b, a, Cantuti Castelvetri et al., 2013). The disease is typified by abnormal axonal transport and severe axonal loss, which is accompanied by astrogliosis (Jesionek-Kupnicka et al., 1997, Castelvetri et al., 2011). Metabolic alterations in astrocytes have been reported in a mouse model of Krabbe disease, which included increased glutamine levels and upregulation of lactate-specific monocarboxylic acid transporters (Meisingset et al., 2013). Additionally, primary astrocytes isolated from Krabbe disease mice displayed increased prostaglandin receptor (DP1 and DP2) expression (Mohri et al., 2006) and IL-6 production was elevated in reactive astrocytes in the CNS (LeVine and Brown, 1997). However, the functional significance of these alterations in astrocyte properties in Krabbe disease and how they may impact neuron survival or function remain unknown.

Microglial activation has also been reported in patients with Krabbe disease, which is consistent with a prominent neuroinflammatory response (Smith et al., 2014). This robust inflammatory response likely results from pronounced cell loss and release of danger-associated molecular patterns (DAMPs) from damaged/dying neurons that can trigger inflammatory pathways, which in turn, further exacerbate neuron damage. Indeed, psychosine has been reported to exert inflammatory and apoptotic effects in glia (Giri et al., 2002).

Sandhoff disease

Sandhoff disease is caused by a deficiency in β-hexosaminidases A and B, resulting in the excessive lysosomal accumulation of GM2 gangliosides and oligosaccharides containing glucosamine residues (Itoh et al., 1984). There are three forms of Sandhoff disease, namely infantile, juvenile, and adult onset (O'Dowd et al., 1986). The infantile form is the most aggressive and typically presents between 2–9 months age, with death occurring before 3 years (O'Dowd et al., 1986). The juvenile form of Sandhoff disease is less common than the infantile variant, with clinical symptoms evident between the ages of 3–10 years, which include organomegaly, bone deformations, and CNS manifestations, such as speech disabilities, cerebral ataxia, and severe psychomotor disturbances (O'Dowd et al., 1986). Neuropathological abnormalities associated with Sandhoff disease include prominent cerebellar atrophy and ventricular dilatation. Histologically, neurons harbor membranous cytoplasmic bodies (MCBs) formed by the accumulation of GM gangliosides and other lipopigments in the lysosome (Itoh et al., 1984). Lectin staining has revealed the prominent accumulation of complex carbohydrates, such as N-acetylglucosamine, in astrocytes (Alroy et al., 1988) and MCBs are also observed in children with Sandhoff disease (Itoh et al., 1984). Astrogliosis is a prominent feature of Sandhoff disease, although the functional implications of reactive astrocytes remain unknown (Myerowitz et al., 2002). An earlier report examining primary astrocytes isolated from a mouse model of Sandhoff disease demonstrated increased proliferation that was associated with elevated ERK phosphorylation and sphingosine-1-phosphate (S1P) synthesis (Kawashima et al., 2009). These changes in astrocytes were dependent on GM2 ganglioside accumulation within the lysosome. Additionally, a direct relationship between S1P metabolism and reactive astrocytosis has been reported in a mouse model of Sandhoff disease, where the deletion of sphingosine kinase (which synthesizes S1P) or sphingosine-1 phosphate receptor reduced astrocyte proliferation and reactive astrocytosis (Wu et al., 2008). Interestingly, S1P has recently emerged as a key neuroinflammatory mediator in multiple sclerosis and is being explored as a potential therapeutic target to attenuate disease severity (Brinkmann, 2009, Graler, 2010, Chun and Brinkmann, 2011). Accordingly, astrocytes from Sandhoff disease mice produced the chemokine macrophage-inflammatory protein 1α (MIP-1α) (Wu and Proia, 2004), which when deleted improved the neurological status and lifespan of these animals (Wu and Proia, 2004). These observations support a pathological role for astrocytes in neuronal dysfunction and Sandhoff disease progression.

Multiple sulfatase deficiency

Multiple sulfatase deficiency (MSD) is caused by a mutation in sulfatase modifying factor 1 (Sumf1) that results in post-translational defects in lysosomal sulfatases and the pathological accumulation of mucopolysaccharides (Austin, 1973, Eto et al., 1980). There are three types of MSD, namely neonatal, late-infantile, and juvenile (Busche et al., 2009). The infantile form of MSD is the most aggressive, with symptoms beginning soon after birth. Clinical manifestations include coarsened facial features, ichthyosis, deafness, splenomegaly, and hepatomegaly (Burk et al., 1984, Macaulay et al., 1998, Diaz-Font et al., 2005). Children with MSD develop leukodystrophy, leading to movement disorders and developmental delay with occasional seizures (Guerra et al., 1990, Incecik et al., 2013). The late-infantile form is the most common type of MSD. These children have normal cognitive development in early

childhood but experience a rapid decline in motor and cognitive abilities that are attributed to progressive leukodystrophy (Kohlschutter, 2013). Neuroimaging studies have revealed periventricular lesions extending into the corpus callosum and brain stem (Guerra et al., 1990). MSD is also typified by extensive demyelination, with the accumulation of metachromatic material composed of cholesterol and galactolipid pigments in CNS glia and peripheral macrophages (Annunziata et al., 2007). A recent study demonstrated that the targeted deletion of Sumf1 in astrocytes using a Cre-Lox mouse model resulted in severe lysosomal storage material deposition and cortical neuron loss *in vivo* (Di Malta et al., 2012b). Sumf1-deficient astrocytes also failed to promote the survival and function of wild type neurons, suggesting a non-cell autonomous mechanism for neurodegeneration. This study was the first to demonstrate that astrocytes play a key role in MSD neuropathology (Di Malta et al., 2012b); however, the mechanisms responsible for astrocyte-mediated neuronal dysfunction and death remain to be identified.

LSDs associated with other lysosomal defects

Niemann-Pick Type C

Niemann-Pick type C (NPC) is caused by mutations in one of two genes, NPC1 or NPC2, which manifest as severe abnormalities in lipid trafficking (Lloyd-Evans and Platt, 2010). Both NPC1 and NPC2 are predicted to encode proteins involved in cholesterol homeostasis, which accounts for cholesterol and glycosphingolipid accumulation within the lysosome (Palmer et al., 1985, Sokol et al., 1988, Zervas et al., 2001a, Zervas et al., 2001b, Zhou et al., 2011, Mengel et al., 2013, Platt et al., 2014). NPC affects both peripheral organs and the CNS, with symptoms ranging from splenomegaly and hepatomegaly to neurological abnormalities, including psychomotor disturbances, ataxia, and seizures (Lloyd-Evans and Platt, 2010, Mengel et al., 2013). Neuroimaging studies have revealed diffuse cerebral atrophy and white matter changes (Palmer et al., 1985). In chronic progressive cases, neurofibrillary tangles similar to those in Alzheimer's disease (AD) have been reported (Ohm et al., 2003). Astrocyte and microglial activation is also associated with NPC (Patel et al., 1999, German et al., 2002, Suzuki et al., 2003), where astrocytes exhibit reduced gap junction communication and mitochondrial dysfunction (Saez et al., 2013). Increased levels of IL-1β as well as increased ApoE, a genetic risk factor for Alzheimer's disease, have been reported in animals models of NPC (Yan et al., 2014). Consistent with this study, increased expression of amyloid precursor protein (APP) as well as β- and γ-secretase were found in reactive astrocytes in mice with NPC disease (Kodam et al., 2010) suggesting an association between NPC and AD.

Neuronal ceroid lipofuscinosis (NCL)

Neuronal ceroid lipofuscinosis (NCL), commonly referred to as Batten disease, represents a family of disorders caused by mutations in ceroid lipofuscinosis (CLN) genes (Getty et al., 2007, Aberg et al., 2009). To date, mutations in 14 different CLN genes have been identified that are broadly classified into infantile, late-infantile, juvenile, and adult onset forms (Aberg et al., 2009, Lebrun et al., 2011). The childhood forms of Batten disease are characterized by blindness, behavioral deficits, seizures, and progressive cognitive and motor impairment that leads to premature death (Sinha et al., 2004, Cotman et al., 2013). A histopathological

hallmark of all NCLs is the lysosomal accumulation of autofluorescent lipopigments and proteins; however, the structural presentation of inclusion material varies according to each disease type (Palmer et al., 1986). Biochemical characterization of storage material has also identified lipophilic proteins, including subunit C of mitochondrial ATP synthase (SCAMS, primarily in Juvenile NCL) or sphingolipid pigments (in other forms of NCL) (Pardo et al., 1994, Goebel et al., 1999, Fossale et al., 2004).

Infantile NCL (INCL) is the most aggressive NCL form, with a life expectancy of 2–6 years (Hawkins-Salsbury et al., 2013). INCL is caused by a mutation in CLN1, which encodes for palmitoyl protein thioesterase (PPT1), an enzyme responsible for the cleavage of long-chain fatty acid residues on several proteins containing cysteine moieties (Vesa et al., 1995, Hofmann et al., 1997). Clinical symptoms of INCL can manifest as early as 6 months of age, which rapidly progress to severe motor and cognitive deficits, seizures, and premature death (for review see (Cotman et al., 2013). Late-infantile NCL (LINCL) is caused by mutations in CLN2 that encodes the lysosomal enzyme tripeptidyl peptidase I (TPPI), which cleaves tripeptides from the terminal amine groups of partially unfolded proteins (Sleat et al., 1997, Sleat et al., 1999). Juvenile NCL (JNCL) results from mutations in the CLN3 gene (for review see (Cotman et al., 2013). The precise function of CLN3 remains unknown; however, based on functional analysis in yeast and mammalian cell culture models, CLN3 has been predicted to regulate lysosomal acidification, endocytic and vesicle trafficking, and proper maintenance of mitochondrial function (Pearce et al., 1999, Kim et al., 2003, Luiro et al., 2004). Similar to INCL and LINCL, JNCL also presents with visual impairment, seizures, and progressive cognitive and motor decline, but with an advanced onset, typically between 5–10 years of age (Cotman et al., 2013). Astrocyte and microglial involvement in NCLs will be discussed in more detail in a later section.

NEURODEGENERATION IN LSDs

Many LSDs are associated with neurodegeneration, which manifests as moderate to severe neuronal death in multiple brain regions, including the thalamus, cerebral cortex, hippocampus and cerebellum (Folkerth, 1999, Prada and Grabowski, 2013). Neuron loss is usually accompanied by reactive astrocytosis that has been suggested to further exacerbate neuronal abnormalities (Jesionek-Kupnicka et al., 1997, Vitner et al., 2010b). While the mechanisms responsible for neurodegeneration in many LSDs is not completely understood, the abnormal accumulation of lysosomal storage material due to defective degradation mechanisms was originally thought to contribute to neuronal loss in LSDs (Kiselyov et al., 2007, Settembre et al., 2008, Lieberman et al., 2012) as well as in other neurodegenerative disorders typified by protein aggregation, such as AD and Parkinson’s Disease (PD) (Matsuda and Tanaka, 2010, Tan et al., 2014). However, this possibility has recently been called into question in LSDs based on the finding that lysosomal storage material accumulation is typically widespread in neurons throughout the brain, yet only select neuron populations die. Nevertheless, neurons are post-mitotic and unable to eliminate unwanted organelles and macromolecules by cell division. Therefore, neurons rely heavily on functional lysosomes to efficiently clear these substances by a process referred to as autophagy. Autophagy delivers cytosolic components to lysosomes by enveloping them into autophagosomes, which fuse with lysosomes to facilitate the degradation of vesicle contents

(Nixon, 2006, Lieberman et al., 2012). Autophagic defects have been reported in several LSDs, including Pompe disease, MSD, NPC, Gaucher disease, and NCLs (Lieberman et al., 2012), which have been suggested to contribute to neurodegeneration. Additionally, lysosomal membrane permeability (LMP) has been demonstrated in several LSDs, including late-infantile NCL (Micsenyi et al., 2013) and mucopolysaccharidosis type I (Pereira et al., 2010). Aberrant autophagy has been suggested as a link to LMP, which has been shown to enhance protein aggregates and may trigger neurodegeneration (Rodriguez-Muela et al., 2015).

Several lines of evidence also support mitochondrial dysfunction in CNS cells in various LSDs, including Gaucher disease, MSD, NPC, and mucopolysaccharidoses (Yu et al., 2005, Osellame and Duchen, 2014). In addition, perturbed mitochondrial Ca^{2+} homeostasis has also been observed in the aforementioned LSDs, including decreased Ca^{2+} buffering capacity and reduced ATP production as well as mitochondrial fragmentation (Kiselyov et al., 2007, de Pablo-Latorre et al., 2012, Chandrachud et al., 2015). A reduction in mitochondrial membrane potential and concomitant decrease in ATP was shown in a mouse model of NPC1 (Yu et al., 2005). Decreased oxygen consumption and mitochondrial electron transport chain enzymes have been reported in neurons from a mouse model of JNCL ($CLN3^{-/-}$) (Luiro et al., 2006). Similarly, enlarged mitochondria were observed in a cerebellar neuronal granular cell line derived from JNCL mice (Fossale et al., 2004); however, it should be noted that this cell type is not lost in the disease. Mitochondrial dysfunction in astrocytes has also been observed in several LSDs, including Gaucher, GM1-gangliosidosis, and NPC (Takamura et al., 2008, Osellame and Duchen, 2014). Therefore, mitochondrial abnormalities may represent a common feature of LSDs, raising the possibility that an energy crisis could be one mechanism responsible for the neurodegenerative process. The nature and purported functions of reactive astrocytes in the context of LSDs will be discussed in greater detail in the following section.

DO REACTIVE ASTROCYTES CONTRIBUTE TO NEURONAL LOSS IN LSDs?

Reactive astrocytosis occurs in response to a variety of insults/stimuli, which can accompany either acute (i.e. traumatic brain injury, cerebral ischemia) or chronic neurological conditions (i.e. AD, PD, and LSDs; for review see (Burda and Sofroniew, 2014, Pekny and Pekna, 2014). While several studies have reported extensive neuronal loss in humans and animal models of LSDs (Folkerth, 1999, Prada and Grabowski, 2013), the involvement of other CNS cells, particularly astrocytes, in the pathogenesis of LSDs have not been extensively investigated. Reactive astrocytosis is a common sequelae in a large number of LSDs; however, its functional consequences remain unclear. It is possible that astrocytes respond to neuronal dysfunction in a protective manner in an attempt to restore homeostasis. Alternatively, activated astrocytes may exacerbate neuron loss by diverting their homeostatic functions (i.e. glutamate uptake and metabolism, pH/ion buffering) towards other pathways that are not conducive to neuron survival, as they also express the same genes that are mutated in neurons. Numerous signals can elicit reactive astrocytosis; however, in the context of LSDs, danger-associated molecular patterns (DAMPs) released from damaged or dying cells appear to represent the most physiological relevant stimuli to trigger astrocyte acitvation (Vincent et al., 2007).

Upon activation, astrocytes undergo a morphological transformation and alter their gene expression profiles. A major hallmark of reactive astrocytosis is increased expression of the intermediate filament proteins glial fibrillary acidic protein (GFAP) and vimentin (for review, see (Hol and Pekny, 2015). The precise function of augmenting these proteins is not clear; however, studies have shown that both GFAP and vimentin participate in limiting the extent of CNS damage by sequestering affected areas following stroke or spinal cord injury (Pekny et al., 1999, Li et al., 2008). Along these lines, a recent study has reported that reactive astrocytes play a protective role in infantile NCL (Macauley et al., 2011). Specifically, CLN1/GFAP/vimentin triple mutant mice displayed more aggressive disease progression than WT animals, which correlated with increased neuroinflammation (Macauley et al., 2011, Shyng and Sands, 2014). Because of the selectivity of GFAP and vimentin to astrocytes, protective responses were predicted to be astrocyte-derived; however, it remains possible that additional factors may have contributed to the accelerated disease phenotype in these mice. For example, it is known that astrocytes display a significant degree of crosstalk with neurons and even microglia (Bezzi et al., 2001, Liu et al., 2011). Therefore, if astrocyte function was impacted by the loss of GFAP and vimentin in the context of CLN1 mutation, this would have worsened neuron survival and contributed to more aggressive disease, although this possibility remains speculative.

Despite the fact that numerous LSDs are typified by reactive astrocytosis, the stimuli responsible for astrocyte activation are not completely known. Although intrinsic changes resulting from the accumulation of lysosomal material could be one trigger, it is possible that non-autonomous signals from neighboring cells, such as neurons or microglia, could drive astrocyte activation by sensing DAMPs released from dysfunctional or dying cells (Figure 1). This possibility is feasible, since inflammatory mediators and other DAMPs are known to induce reactive astrocytosis in various neurological conditions (Vincent et al., 2007). Relevant to LSDs, microglia in a mouse model of Juvenile Batten Disease (JNCL) have been shown to exist in a “primed” state, producing exaggerated levels of numerous proinflammatory mediators in response to DAMPs, whereas wild type microglia were relatively non-responsive (Xiong and Kielian, 2013). By extension, these microglial-derived inflammatory mediators can trigger astrocyte activation to establish a perpetual inflammatory cycle that can induce neuronal death under chronic conditions. Indeed, CLN3 mutant neurons were more susceptible to cytokine-induced death compared to WT neurons (Xiong and Kielian, 2013). It will be important to investigate the other consequences of CLN3 deficiency for astrocytes and microglia and the potential consequences this may have for neurons. This will be achieved with the use of CLN3 conditional knockout mice that are currently in development, where CLN3 is selectively excised in astrocytes or microglia using glial-specific Cre-deleter lines.

In terms of the potential molecular mechanisms whereby LSDs alter astrocyte properties and how these changes affect neuronal survival or function, we can look to other neurodegenerative diseases for examples, since as mentioned above, common themes have recently emerged. For example, various signaling pathways have been shown to contribute to reactive astrocytosis in acute and chronic neurological conditions (Pekny and Nilsson, 2005, Burda and Sofroniew, 2014). These include JAK/STAT3 signaling and ERK1/2 phosphorylation (Sriram et al., 2004). Notably, JAK/STAT3 activation was observed in a

mouse model of Sandhoff disease ($Hexb^{-/-}$) that was mediated by microglial-derived TNF-α production. Inhibition of TNF-α in Hexb/Tnf-α double knockout mice significantly inhibited astrocyte activation and reduced neuronal death. These changes coincided with significantly increased lifespan, enhanced sensorimotor coordination, and improved neurological function. Interestingly, these improvements in Hexb/Tnf-α double knockout animals were not accompanied by alterations in ganglioside accumulation in neurons (Abo-Ouf et al., 2013). Likewise, increased ERK phosphorylation was shown in a sheep model of infantile NCL, where reactive astrocytes are a prominent feature and associated with aggressive neurodegeneration (Kanninen et al., 2013).

Many LSDs have been associated with defects in autophagy (Kiselyov et al., 2007, Settembre et al., 2008, Lieberman et al., 2012), which could represent another pathway to induce astrocytosis, since cells are unable to clear cellular debris (Lee et al., 2009, Di Malta et al., 2012b). In addition, autophagic inhibition could lead to cytoplasmic DAMP release from damaged/senescent organelles to trigger astrocyte activation (Figure 1). Consistent with this tenet, increased lactosylceramide (LacCer), a glycolipid shown to be dysregulated in mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, was shown to activate astrocytes and cause neurodegeneration (Chen et al., 1999). Inhibition of excessive LacCer formation not only reduced astrocytosis but also diminished neurodegeneration in these animals (Chen et al., 1999). Numerous LSDs, including NPC, GM1 gangliosidosis, acid lipase deficiency, and mucopolysaccharidoses, are typified by lysosomal LacCer accumulation (Di Malta et al., 2012b) and it is intriguing to consider whether this could represent a mechanism to trigger astrocyte activation. Finally, an autophagic block could also create nutrient and energy stresses on the cell that could elicit reactive astrocytosis.

Additional molecules that accumulate within astrocytes in various LSDs may also contribute to astrocyte activation and associated pathology. For example, ceramide species known to accrue in select LSDs can induce reactive astrocytosis (Bassi et al., 2006) by activating NF-κB (Calatayud et al., 2005) and MAPKs (Oh et al., 2006). In addition, ceramides have well-described pro-apoptotic activity (Jatana et al., 2002, Oh et al., 2006), which could contribute to astrocyte loss during more advanced stages of disease, although this remains speculative and has not yet been demonstrated in any LSD to date. Cathepsin D is another molecule that is elevated in astrocytes during Gaucher disease and was implicated in astrocyte dysfunction (Choi et al., 2002). Furthermore, astrocytes from Sandhoff disease mice have been shown to possess inflammatory activity via chemokine production (Wu and Proia, 2004) that may amplify CNS inflammation and collateral neuronal damage. To date, only a few studies have directly demonstrated a role for reactive astrocytes in neurodegeneration in select LSDs. As mentioned earlier, a recent report showed that targeted deletion of Sumf1 (mutation in MSD) in astrocytes using a Cre-Lox mouse model resulted in severe lysosomal storage and induced cortical neuron loss *in vivo* (Di Malta et al., 2012b, a). Sumf1-deficient astrocytes also failed to promote the survival and function of wild type neurons, suggesting a non-cell autonomous mechanism for neurodegeneration. Indirect evidence also suggests that astrocyte dysfunction in LSDs may exert detrimental effects on neurons. Such information has been largely derived from targeted gene therapy, where the re-insertion of deficient genes into astrocytes was shown to limit neurodegeneration. For example, NPC1 gene transduction into astrocytes

was shown to enhance survival, decrease neuronal cholesterol accumulation, and reduce neurodegeneration in a NPC mouse model (Zhang et al., 2008). Likewise, retroviral-mediated transduction of the human GBA gene into astrocytes and oligodendrocytes in Twitcher mice was shown to correct the neuronal phenotype in these animals (Luddi et al., 2001).

Additionally, several lines of evidence indicate that reactive astrocytosis precedes neuronal loss in some LSDs, including various forms of Batten disease. For example, studies have shown early prominent astrocyte activation, as indicated by increased GFAP expression, in JNCL mouse models that predates neuronal loss in these mice that is not evident until around 12 months of age (Pontikis et al., 2004, Burkovetskaya et al., 2014). Likewise, a sheep model of variant late-infantile NCL (CLN6) displays overt astrocyte activation in several brain regions prior to any neurodegeneration (Oswald et al., 2005). Astrocyte activation also precedes neuron loss in other NCL forms, including CLN1 and CLN8 disease (Macauley et al., 2009, Kuronen et al., 2012).

Recent evidence suggests that astrocytes express functional neurotransmitter receptors that actively participate in synaptic transmission at the tripartite synapse (Perea et al., 2009) and also influence neuronal synapses by releasing gliotransmitters (Perea et al., 2009, Araque et al., 2014). One proposed mechanism for astrocyte gliotransmitter release is through hemichannels (HCs; for review see (Bosch and Kielian, 2014, Montero and Orellana, 2015). A HC is composed of a hexameric ring of connexin proteins and constitutes one-half of a gap junction channel. HCs form gap junctions when they align with adjacent HCs in neighboring cells; however, HCs can also be formed by pannexins that are incapable of forming gap junctions (Saez and Leybaert, 2014). HCs have been reported to open under both physiological and pathological conditions to facilitate the release of various small m.w. metabolites and gliotransmitters from astrocytes, including ATP, glucose, glutathione, glutamate, GABA, and D-serine (Giaume et al., 2013, Abudara et al., 2014, Abudara et al., 2015, Montero and Orellana, 2015). Transient HC opening may provide a mechanism for fine tuning changes in intracellular and extracellular molecular gradients across the astrocyte membrane; however, chronic HC activity can have catastrophic consequences by dissipating CNS chemical gradients that require a significant energetic cost to establish (Saez et al., 2013, Bosch and Kielian, 2014). For example, opening of connexin 43 hemichannels in astrocytes and subsequent release of ATP and glutamate has been shown to induce neuronal death during hypoxic conditions (Orellana et al., 2011a), in an *in vitro* slice culture model of Alzheimer's disease (Orellana et al., 2011b), as well as during HIV and bacterial infection (Karpuk et al., 2011, Orellana et al., 2014). In the context of LSD, astrocyte HC activity was transiently increased in acute brain slices derived from a mouse model of JNCL at an early postnatal age (1 month) that significantly preceded neuronal loss, which occurs around 12 months in this model (Burkovetskaya et al., 2014). Interestingly, the expression of astrocyte-specific glutamate transporters and glutamine synthetase was significantly decreased with increasing age of CLN3 mutant mice, suggesting a decline in astrocyte function. This possibility was reinforced by electrophysiological findings in acute brain slices, demonstrating abnormalities in resting membrane potential and conductance in CLN3 mutant astrocytes (Burkovetskaya et al., 2014). It is noteworthy that in light of these changes, astrocytes in the CLN3 mutant mouse were shown to be activated as typified by

increased GFAP expression. Blockade of HC activity using the novel carbenoxolone-based inhibitor INI-0602 enhanced gap junction communication and led to significant reductions in lysosomal storage material in the brains of CLN3 mutant mice (Burkovetskaya et al., 2014). Collectively, this supports the premise that astrocyte dysfunction likely influences neuropathology in LSDs, although it remains to be determined whether this is a universal phenomenon or restricted to specific LSDs.

SIMILARITIES BETWEEN LSDs AND PARKINSON'S DISEASE

While LSDs are a distinct class of disorders resulting from inborn errors in lysosomal metabolism, neuropathological similarities between LSDs and PD exist (for review see (Deng et al., 2014). For example, clinical symptoms such as bradykinesia, rigidity, and tremors characteristic of PD are also found in some of the LSDs, including JNCL (Aberg et al., 2000, Valadares et al., 2011). Further, extensive reports describing astrocyte activation (Schneider and Denaro, 1988, Blunt et al., 1992, Renkawek et al., 1999, Episcopo et al., 2013) and dysfunction in PD, including aberrant autophagy (Osellame et al., 2013), proteasomal defects (Jansen et al., 2014) and neuroinflammation (Tilleux and Hermans, 2007) are also common features of various LSDs (Jesionek-Kupnicka et al., 1997, Pontikis et al., 2004, Vitner et al., 2010b, Di Malta et al., 2012a, b, Burkovetskaya et al., 2014). Additionally, both JNCL and PD share certain similarities in the brain regions affected, including nigrostriatal pathology, as well as abnormal substrate accumulation, either lysosomal storage or α-synuclein, respectively (Jarvela et al., 1997, Weimer et al., 2007). There is also growing evidence that heterozygous carriers of Gaucher and NPC mutations have increased risk for developing PD, which clearly highlights a link between these diseases (Neudorfer et al., 1996, Volders et al., 2002, Halperin et al., 2006, Sidransky et al., 2009b, Goker-Alpan et al., 2012). Indeed, a multicenter analysis examining GBA mutations in PD patients revealed an odds ratio of 5.43 compared to controls. PD patients harboring a GBA mutation had an earlier disease onset (on average 4 years earlier) and were more likely to experience atypical clinical disease, making GBA mutations among the most common genetic risk factors for PD identified to date (Sidransky et al., 2009a). Similar to GD, patients with Niemann-Pick display α-synucleopathy (Coleman et al., 1988, Josephs et al., 2004, Saito et al., 2004).

LSDs and PD also share attributes at the subcellular level, suggesting that some aspects of pathology may overlap. Specifically, both disorders display evidence of disturbed autophagy-lysosomal pathways, proteasome defects, mitochondrial abnormalities, and intracellular accumulation of macromolecules (Pan et al., 2008, Osellame and Duchen, 2014). Other features, such as glial activation and selective neuron loss in specific brain regions are also common between LSDs and PD (Aberg et al., 2000, Wong et al., 2004). Therefore, it is possible that treatment strategies designed for PD may also exert beneficial effects to counteract neurological abnormalities in patients with specific LSDs, although this remains to be determined.

CONCLUDING REMARKS

Lysosomal storage diseases are debilitating disorders caused by inborn errors in lysosomal proteins. Numerous LSDs are associated with CNS pathology, with prominent neurodegeneration typically occurring in early childhood, which reduces life expectancy. Unfortunately, there is no cure for these diseases, which has resulted in aggressive attempts for gene/enzyme replacement therapy to counteract the pathological consequences of these diseases. Available evidence suggests that astrocyte activation is an early indicator of CNS pathology in these disorders, which conceivably contributes to neurodegeneration in later stages of disease progression. However, whether astrocyte dysfunction is a primary cause of neuronal loss or rather a consequence of reactivity to diseased neurons in the context of LSDs remains the proverbial “chicken and the egg” question. Recent studies employing selective enzyme/gene replacement strategies in astrocytes have revealed significant reductions in neuronal loss as well as improved survival, which strongly suggest that neurodegeneration in LSDs may in part be a consequence of astrocyte dysfunction. However, it remains to be determined if astrocyte involvement in neuronal demise is a universal phenomenon across several LSDs or rather, is only applicable to select degenerative processes. Nevertheless, targeting glial dysfunction in these LSDs may have a therapeutic benefit, an avenue that is currently being pursued.

Acknowledgments

This work was supported by the National Institute of Neurological Disorders and Stroke (NINDS) 1R21NS084392-01A1 to T.K. The authors thank Dr. Jonathan Cooper at King’s College London for critical review of the manuscript.

ABBREVIATIONS

AD	Alzheimer’s Disease
CNS	central nervous system
DAMP	danger associated molecular pattern
GBA	glucocerebrosidase
GLD	globoid cell leukodystrophy
GFAP	glial fibrillary acidic protein
INCL	Infantile Neuronal Ceroid Lipofuscinosis
JNCL	Juvenile Neuronal Ceroid Lipofuscinosis
LINCL	Late Infantile Neuronal Ceroid Lipofuscinosis
LMP	lysosomal membrane permeability
LSD	lysosomal storage disease
MSD	multiple sulfatase deficiency
NPC	Niemann-Pick type C

PAMP	pathogen associated molecular pattern
PPT1	palmitoyl protein thioesterase
TPP1	tripeptidyl peptidase I
PD	Parkinson's Disease
SCMAS	subunit C mitochondrial ATP synthase

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HIGHLIGHTS

1. Several lysosomal storage diseases (LSDs) are associated with CNS neuron loss.
2. Astrocyte dysfunction is observed in numerous LSDs and is suggested to impact neurodegeneration.
3. Enzyme/gene replacement in astrocytes reduces neuron loss, implicating astrocyte dysfunction in LSD pathology.

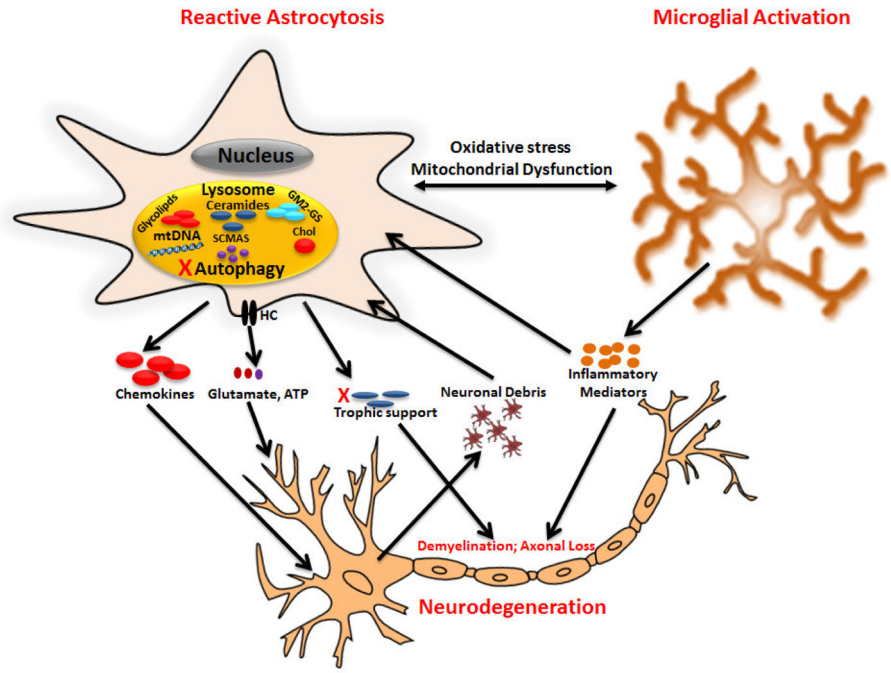

Figure 1. Potential contribution of reactive astrocytes to neurodegeneration in LSDs

Lysosomal dysfunction in astrocytes and microglia likely contributes to neuron death in a non-cell autonomous manner through the release of damaging mediators and/or loss of trophic support. In addition, disruption of lysosomal homeostasis in neurons also regulates cell death in a cell autonomous manner. GM2-GS, GM2-gangliosides, HC, hemichannels, mtDNA, mitochondrial DNA, chol, cholesterol.