Neuronal and microglial cathepsins in aging and age-related diseases

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Abstract

It has been long believed that cathepsins compensate for each other because of their overlapping substrate specificities. However, there is increasing evidence that disturbance of the normal balance of their enzymatic activities is the first insult in brain aging and age-related diseases. The imbalance of cathepsins may further cause age-related neuropathological changes such as accumulation of autophagic vacuoles and the formation of ceroid-lipofuscin leading to neuronal dysfunction and damage. Leakage of cathepsins due to the fragility of lysosomal membranes during aging also contributes to neurodegeneration. Furthermore, the deficiency of cathepsin D has been recently revealed to provoke a novel type of lysosomal storage disease associated with massive neurodegeneration. In these animals, microglia are activated to initiate inflammatory and cytotoxic responses by binding and phagocytosis of storage neurons. Activated microglia also release some members of cathepsins to induce neuronal death by degrading extracellular matrix proteins. Thus the microglial activation possibly through sensing neuronal storage may also be an important causative factor for neurodegeneration in lysosomal storage diseases and age-related diseases such as Alzheimer’s disease. This review describes the pathological roles of neuronal and microglial cathepsins in brain aging and age-related diseases.

Keywords: Cathepsin; Neuron; Microglia; Endosomal/lysosomal system; Ceroid-lipofuscin; Aging; Alzheimer’s disease; Lysosomal storage disease

1. Introduction

A group of proteases in the endosomal/lysosomal proteolytic system is called cathepsin which is derived from the Greek term meaning “to digest” (Willstätter and Bamann, 1929).
Cathepsins are synthesized on membrane-bound ribosomes as N-glycosylated precursors and are transferred into the endoplasmic reticulum and later into the Golgi complex. During transport to the Golgi complex, pro-cathepsins acquire modification of their carbohydrate moieties, which includes the formation of the mannose 6-phosphate (M6P) residues. Following the binding to M6P-specific receptors (MPRs), the enzyme–receptor complexes exit the trans-Golgi network in clathrin-coated vesicles and are transported to the late endosomes (Kornfeld, 1992). Upon fusion with the late endosomes, the dissociation of ligands occurs. The delivery of pro-cathepsins to lysosomes is accompanied by a series of proteolytic cleavages into their mature forms. In addition to a M6P-dependent targeting system, cathepsins can be also targeted to the lysosomes in a M6P-independent mechanism (Glickman and Kornfeld, 1993).

Although the primary function of cathepsins is to degrade proteins by bulk proteolysis in lysosomes, recent results from cathepsin gene knockouts have revealed that cathepsins carry out their specific functions by limited proteolysis of proteins (Saftig et al., 1995; Turk et al., 2000; Reinheckel et al., 2001). It is likely that limited proteolysis is exerted by cathepsins in less acidic intracellular compartments such as early and late endosomes. There is increasing evidence that disturbance of normal balance and extralysosomal localization of cathepsins contribute to neurodegeneration in Alzheimer’s disease, stroke, and lysosomal storage diseases (Cataldo et al., 1990, 1991; Nakanishi et al., 1994, 1997; Nixon, 2000; Koike et al., 2000; Yamashima, 2000). Furthermore, the dysfunction of endosomal/lysosomal system in neurons is closely associated with an activation of microglia which could initiate an inflammatory response to provoke a neurodegeneration (Nakanishi, 2003b). Activated microglia also release some members of cathepsins to induce neuronal death through degradation of extracellular matrix proteins (Nakanishi, 2003a, 2003b). Thus, this review will focus on the pathological roles of neuronal and microglial cathepsins in brain aging and age-related diseases.

2. Cathepsins and brain aging

2.1. Cathepsin alterations during brain aging

Alterations in the concentration and localization of cathepsins in the central nervous system (CNS) have been reported in normal aged brain (Nakamura et al., 1989). We have reported that the levels of cathepsins D and E were significantly increased during normal aging process (Fig. 1A and B) (Nakanishi et al., 1994, 1997). The enzymatic activity of cathepsin B was also increased significantly in the neostriatum of the aged rat but is relatively unchanged in other regions from 2 to 28 months. By contrast, the enzymatic activity of cathepsin L was decreased significantly (approximately 90%) in all brain regions of aged rats (Nakanishi et al., 1994). There were also marked age-related changes in cellular localization and enzymatic activities of cathepsins in peripheral neurons. Cathepsins D, B and L were widely and evenly distributed throughout the cytoplasm as coarse intracytoplasmic granules, whereas they were localized at focal cytoplasmic sites in trigeminal ganglion neurons of aged rats (Fig. 1C and D). The enzymatic activities of cathepsins B and L were decreased significantly (approximately 50%) in aged rats (Amano et al., 1995). Lynch’s group has been motivated
Fig. 1. Age-related changes of cathepsins in CNS and trigeminal ganglion neurons. Staining of cathepsin D in the hippocampal CA1 neurons of 2-month-old (A) and 30-month-old (B) rat, respectively. Staining of cathepsin D in the trigeminal ganglion neuron of 2-month-old (C) and 30-month-old (D) rat, respectively. Immunoreactivities of cathepsin D (E) and their colocalization with autofluorescent lipopigments (F) in cortical neurons of 30-month-old rat. Colocalization of cathepsin D-immunoreactivities and autofluorescent lipopigments was indicated by arrowheads. Double-staining immunohistochemistry of cathepsin E (G) and carboxy-terminal fragments of APP (APP643–695) (H) in the brainstem neurons of 30-month-old rat. Colocalization of immunoreactivities of cathepsin E and APP643–695 was indicated by arrowheads. Scale bars: 10 μm (A–D), 50 μm (E and F), 100 μm (G and H).
by these observations and examined effects of long-term treatment of cysteine protease inhibitors on the hippocampal slice cultures. *N*-CBZ-L-phenylalanyl-L-alanine-diazomethyl ketone, a selective inhibitor of cathepsins B and L, induced increased cathepsin D levels, the accumulation of lysosome-related dense bodies and hyperphosphorylated \( \tau \) fragments, and the formation of meganeurites in the perykarya of CA1 neurons in cultured hippocampal slices (Bednarski and Lynch, 1996; Bednarski et al., 1997). These observations strongly suggest that disturbance of the normal balance of enzymatic activity of cathepsins causes age-related neuropathological changes. However, lysosome-related dense bodies induced by *N*-CBZ-L-phenylalanyl-L-alanine-diazomethyl ketone did not emit autofluorescence, indicating that they do not contain ceroid-lipofuscin, a major type of residual body observed in various types of neurons during the aging process (Bednarski et al., 1997). This contrasts with the observation that intraventricular application of leupeptin, a cystein protease inhibitor, or chloroquine, a general lysosomal inhibitor, in young rats induced the formation of lysosome-associated granular aggregates that closely resemble ceroid-lipofuscin (Ivy et al., 1984).

Upregulation of the endosomal/lysosomal system has also been demonstrated in affected neurons of Alzheimer’s disease brain (Nixon and Cataldo, 1993, 1995; Nixon, 2000). In the senile plaques, the enzymatically active cathepsin D, as well as cathepsins B and L, are present extracellularly at high levels (Bernstein et al., 1989; Cataldo and Nixon, 1990; Cataldo et al., 1991). Furthermore, secondary lysosomes and residual bodies are markedly increased in affected neurons of Alzheimer’s disease brain (Cataldo et al., 1990; Nixon and Cataldo, 1993). The activation of the endosomal/lysosomal system has been suggested to be closely associated with increased production of amyloid \( \beta \) (A\( \beta \)) peptides in sporadic Alzheimer’s disease (Nixon, 2000).

### 2.2. Amyloid precursor protein (APP) metabolism

It is well known that APP is metabolized through two different pathways, secretory and endosomal/lysosomal pathways. In the secretory pathway, \( \beta \)-site APP cleavage enzyme (BACE), a novel transmembrane aspartic protease, has been recently identified as \( \beta \)-secretase (Sinha et al., 1999; Vassar et al., 1999; Yan et al., 1999). On the other hand, cathepsins D and E are considered to influence A\( \beta \) peptides generation within the endosomal/lysosomal system because they have \( \beta \)-secretase activity (Grüninger-Leitch et al., 2000). BACE was also found in early endosomes (Vassar et al., 1999). We have found that cathepsins D and E are colocalized with ceroid-lipofuscin (Fig. 1E and F) and carboxy-terminal fragments of APP (Fig. 1G and H) in CNS neurons of aged rats (Nakanishi et al., 1997). Immunoblot analysis revealed that the molecular sizes of accumulated carboxy-terminal APP fragments were 19 and 22 kDa, suggesting that they might contain an intact A\( \beta \) peptide domain and therefore be amyloidogenic. Matthews et al. (2002) have recently reported that overexpression of MPRs which selectively redirect lysosomal hydrolases to early endosomes increases the generation of A\( \beta \) peptides. It is also known that MPRs are more highly expressed in Alzheimer’s disease brain (Nixon, 2000). These observations strongly suggest that the upregulation of early endosomes as a consequence of increased expression of MPRs are closely associated with enhanced A\( \beta \) peptides production and secretion in Alzheimer’s disease. Although Safﬁg et al. (1996) excluded the possible
involvement of cathepsin D in amyloidogenic processing of APP by utilizing cathepsin D-deficient mice, age-associated factors such as increased expression and endosomal localization may be required for cathepsin D to work as β-secretase (Mathews et al., 2002).

2.3. Lysosomal membrane impermeability

Besides functions inside the endosomal/lysosomal system, there is evidence that some members of cathepsins are also involved in extracellular proteolysis resulting in pathological conditions. Leakage of cathepsins into the cytoplasm is often achieved by the endocytosis of oxidizable substrates that destabilize the lysosomal membranes through lipid peroxidation. It has been proposed that the increased level of cytosolic cathepsin D in the aged rat brain is due to the age-dependent increase in the fragility of the lysosomal membrane (Matsu and Green, 1987; Nakamura et al., 1989). We have previously reported that subcellular fractionation showed that the amounts of cathepsins D and E in the soluble fraction of the aged rat brain were markedly increased as compared with those of the young rat brain, suggesting that these enzymes leaked into the cytoplasm. More recently, leakage of cathepsin D into the cytoplasm of neurons in aged rats is demonstrated by immunoelectron microscopy (Jung et al., 1999). In senile plaques of Alzheimer’s disease brain, lysosomal hydrolases such as cathepsin D distribute in an abnormal extracellular location (Cataldo et al., 1991). In vitro, cathepsin D and β-hexosaminidase are increased in the soluble cytosolic compartment of the cells following treatment with Aβ peptides (Yang et al., 1998).

Some lysosomal cysteine proteases such as cathepsins B, H and L are relatively unstable after leakage from lysosomes, whereas others such as cathepsins D, E, and S are stable even at neutral pH (Bednarski and Lynch, 1996; Turk et al., 2000). Therefore, these enzymes are capable of degrading cytoskeletal proteins and bioactive peptides in the cytoplasm of neurons. Furthermore, there is increasing evidence that some members of cathepsins are directly involved in apoptosis. Cathepsin D has been first reported to play as a final executioner of apoptosis induced by interferon-γ, Fas/APO-1, TNF-α (Deiss et al., 1996), chemotherapeutic agents such as adriamycin and etoposide (Wu et al., 1998), and serum deprivation (Shibata et al., 1998; Isahara et al., 1999). Cathepsin B has been also implicated in the activation of the proinflammatory caspases 1 and 11 (Vancompernolle et al., 1998; Schotte et al., 1998), and the cleavage of Bcl-2 family member Bid (Stoka et al., 2001) which may lead to cytochrome c release from the mitochondria and subsequent caspase activation (Guccio et al., 2000). Taken together, the abnormal localization of cathepsins resulting from the disintegration of lysosomal as well as plasma membranes may contribute to the pathogenesis of age-related neuronal dysfunction and Alzheimer’s disease.

2.4. Upregulation of endosomal/lysosomal system in microglia

In aged rat and Alzheimer’s disease brains, microglia are known to express activation markers such as major histocompatibility complex (MHC) class II molecules, lysosomal membrane marker ED1, and the leucocyte common antigen and CD4 (Perry et al., 1993; Togo et al., 2000). Although the microglial reaction has long been considered as a secondary event following neuronal damage and death, there is increasing evidence that the activation of microglia is closely associated with brain aging and the pathogenesis of Alzheimer’s
disease. Aβ peptides have been reported to induce neuronal death indirectly by activating microglia to produce inflammatory mediators such as nitric oxide (NO), cytokines, and reactive oxygen intermediates (Meda et al., 1995; El Khoury et al., 1996).

Several lines of evidence suggest that activated microglia secrete cathepsins to induce neuronal death. In response to lipopolysaccharide (LPS), there was a substantial increase in cathepsin S activity secreted from both macrophages and microglia (Petanceska et al., 1996). This may suggest that cathepsin S plays a role in degenerative disorders because cathepsin S degrades components of extracellular matrix proteins even at neutral pH. Cathepsin B was also secreted from immortalized murine microglial cell line, BV-2 cells, as the heavy chain form in addition to the proform upon stimulation with LPS (Ryan et al., 1995). More recently, it has been demonstrated that secreted cathepsin B is a major causative factor of microglia-induced neuronal apoptosis (Kingham and Pocock, 2001). We have shown that some cathepsins are closely linked with the proteolytic processing of exogenous antigens and invariant chain of MHC class II molecules through the endosomal/lysosomal system of microglia (Nishioku et al., 2002). Although the precise implication of exogenous antigen presentation in the CNS is not fully understood, inflammatory cytokines secreted from activated helper T cells and microglia activated through their interaction may contribute to the tissue damage and/or repair. Therefore, increased levels of cathepsins in activated microglia distributed especially in the white matter of aged rat (Nakanishi et al., 1994) and Alzheimer’s disease brain (Bernstein and Wiederanders, 1994; Yoshiyama et al., 2000) may have some pathological significance.

2.5. Degradation of Aβ peptides in lysosomes

Cathepsin D has been suggested to be responsible for the intracellular clearance of Aβ peptides in human and rat brains (Hamazaki, 1996; McDermott and Gibson, 1996). Aβ peptides are taken up predominantly by microglia via class A scavenger receptors and class B scavenger receptor type I (Paresce et al., 1996; Husemann et al., 2001). Then Aβ peptides are accumulated and degraded in the lysosomes of microglia (Paresce et al., 1997). Importantly, pepstatin A has been reported to inhibit the degradation of Aβ peptides in microglia (Kakimura et al., 2002). These observations strongly suggest that phagocytosed Aβ peptides are mainly degraded by cathepsin D in lysosomes of microglia. It is also noteworthy that immunization with Aβ peptides has been demonstrated to reduce Aβ peptides in transgenic mice with Aβ plaques (Schenk et al., 1999). Thus, the phagocytosis and subsequent degradation of Aβ peptides by microglia may play a pivotal role in a strategy for the immunotherapy of Alzheimer’s disease.

3. Cathepsins and lysosomal storage diseases

3.1. Cathepsin D-deficient mice

To gain more insight into functions of cathepsin D, mice deficient in cathepsin D were generated by gene targeting (Safar et al., 1995). The homozygous mutant mice developed a progressive atrophy of the intestinal mucosa and a profound destruction of lymphoid tissues.
Although the mutant mice could develop normally during the first 2 weeks, they stopped thriving in the third week, decreased in weight, and then died between 25 and 27 days. At the cellular level, however, lysosomal bulk proteolysis was maintained in these mice. It was concluded that the essential functions of cathepsin D depend on limited proteolysis of biologically active proteins such as growth factors rather than on bulk degradation of proteins in lysosomes.

During the course of our studies on morphological as well as functional changes in CNS neurons of cathepsin D-deficient mice, we noticed that these animals showed neurological phenotypes such as seizures and blindness near the terminal stage. The most striking feature found in the CNS was a profound storage of autophagosome/autolysosome-like bodies with part of the cytoplasm, granular osmiophilic deposits, and fingerprint profiles (Koike et al., 2000). Almost all neurons especially in the cerebral cortex and thalamus contained large autofluorescent bodies, indicating the accumulation of ceroid-lipofuscin in the lysosomal structures (Fig. 2A and B). These ceroid-lipofuscin loaded lysosome contained subunit c of mitochondrial F1F0-ATP synthase, a common storage material of neuronal ceroid lipofusinosis (NCL) except for the infantile form of NCL. Interestingly, however, the protein and activity levels of tripeptidyl peptidase I, whose deficiency causes late-infantile NCL, were increased in cathepsin D-deficient mouse brain (Koike et al., 2000). These observations strongly suggest that the loss of cathepsin D activity causes a novel type of lysosomal storage disease associated with massive neurodegeneration.

3.2. Activated microglia-induced inflammation in lysosomal storage diseases

We have observed a marked accumulation of morphologically transformed microglia exhibiting expanded and round cell bodies with a few thick processes especially in the cerebral cortex and thalamus near terminal stage of cathepsin D-deficient mice (Fig. 2C). The morphological transformation of microglia may be caused by binding and uptake of neurons laden with large autofluorescent bodies (Fig. 2D and E). Furthermore, there is a prominent expression of inducible nitric oxide synthase (iNOS) in both morphologically transformed microglia and peripheral macrophages in cathepsin D-deficient mice (Nakanishi et al., 2001). NO and the superoxide anion, which is generated in mitochondria, react rapidly to form a peroxynitrite anion. This, in turn, generates highly toxic hydroxyl radicals and hydrogen peroxide. Although NO is synthesized from l-arginine by NOS, iNOS is thought to be the isofrom that produces the large quantities of NO that can result in tissue damage or death.

To directly address the possible involvement of NO in tissue damage and neuronal death in cathepsin D-deficient mice, we examined effects of l-N(ω)-nitro-arginine methyl ester (l-NAME), a potent competitive NOS inhibitor and S-methylisothioura hemisulfate (SMT), an iNOS inhibitor. Chronic treatment with l-NAME or SMT significantly decreased the total number of terminal dUTP nick-end labeling (TUNEL)-positive cells counted in the thalamus of cathepsin D-deficient mice (Nakanishi et al., 2001). In the course of these experiments, we unexpectedly found that chronic treatment with l-NAME or SMT markedly ameliorated a severe hemorrhage-necrotic appearance of the small intestine and atrophic changes of the ileal mucosa of cathepsin D-deficient mice. Therefore, the activated microglia/macrophage-induced inflammatory response is considered to be a major causative factor for pathological changes in the CNS and the small intestine of cathepsin D-deficient mice.
Fig. 2. Accumulation of ceroid-lipofuscin in CNS neurons of 24-day-old cathepsin D-deficient mice and phagocytosis by microglia. Autofluorescent lipopigments accumulated in thalamic neurons of the wild-type littermate (A) and cathepsin D-deficient mouse (B), respectively. (C) Accumulation of activated microglia stained with F4/80 in the thalamus of cathepsin D-deficient mouse. (D) Engulfment of neurons that were laden with large autofluorescent bodies (orange) by microglia labeled by F4/80 (green) in the thalamus of cathepsin D-deficient mouse. (E) Electron micrograph of microglia (m) attached to neuron (n) laden with autophagosome–autolysosome-like bodies in the cerebral cortex of cathepsin D-deficient mouse. Scale bars: 30 μm (A and B), 20 μm (C and D), 4.0 μm (E).
Our hypothesis for a mechanism underlying activation of microglia and subsequent massive neuronal death in the CNS caused by cathepsin D-deficiency is summarized in Fig. 3. When cathepsin D activity is deficient, hydrophobic proteolipids such as subunit c of mitochondrial F₁F₀-ATP synthase are first accumulated in lysosomes. These storage materials further facilitate the formation of ceroid-lipofuscin especially in lysosomes of CNS neurons leading to neuronal dysfunction and damage. By binding and phagocytosis of these storage neurons, microglia are activated to produce NO through iNOS. Microglia may be also activated and/or primed through their own accumulation of proteolipids due to cathepsin D-deficiency. Finally, the sustained and high levels of NO released from activated microglia initiate an intensive inflammatory response in the CNS leading to secondary neuronal damage.

Bone marrow transplantation (BMT) has emerged as a potential treatment for some types of lysosomal storage diseases. It has been shown that bone-marrow-derived monocytes/macrophages can cross the blood–brain barrier and become perivascular macrophages and microglia (Eglitis and Mezey, 1997; Ono et al., 1999; Priller et al., 2001). The secretion of lysosomal enzymes from microglia/macrophages derived from hematopoietic donor cells and uptake by surrounding brain cells via M₆P receptor-mediated endocytosis are proposed as the basis for BMT therapy for lysosomal storage diseases. However, it has been recently reported that microglia/macrophages secrete lysosomal enzymes such as arylsulphatase A and cathepsin D, which are incompetent for M₆P receptor-dependent uptake by brain cells due to the lack of M₆P residues (Muschol et al., 2002). Furthermore, BMT has been reported to extend the lifespan and ameliorate neurologic symptoms of Sandhoff disease mice without a clear reduction of neuronal GM₁ ganglioside storage (Norflus et al., 1998; Wada et al., 2000). Furthermore, the involvement of activated microglia in the pathogenesis of lysosomal storage diseases has been also suggested in other mouse models: metachromatic leukodystrophy (Hess et al., 1996), Sandhoff disease (Wada et al., 2000), Niemann-Pick disease type C (German et al., 2002), and mucopolysaccharidoses I and IIIB (Ohmi et al., 2003). Taken together, it is likely that the pathogenesis of these diseases is dominated by activated microglia-induced inflammation rather than lysosomal storage due to the deficiency of lysosomal enzymes. Furthermore, infiltration of blood-born microglial precursors after BMT may improve neuronal pathology by a mechanism other than supplying the missing enzymes.

3.3. White Swedish Landscape sheep

Tyynelä et al. (2000) have shown a novel form of NCL, congenital ovine NCL (CONCL) arising from a naturally occurring cathepsin D mutation. CONCL was observed in a flock of White Swedish Landscape sheep maintained on an experimental farm in Northern Sweden. In CONCL lambs, a single nucleotide mutation in the cathepsin D gene is substituted by a conserved active-site aspartate by asparagines at position 295 (Asp → Asn) resulting in a catalytically inactive protein. These animals show some phenotypes similar to those of cathepsin D-deficient mice such as neuronal death in the cerebral cortex and neuronal storage of autofluorescent granules. The activity of tripeptidyl peptidase I was also elevated. However, there are several differences between CONCL lambs and cathepsin D-deficient mice. Unlike cathepsin D-deficient mice, the newborn CONCL lambs do not exhibit any pathological changes in the lymphoid tissues and ileal mucosa. On the other hand, CONCL
Fig. 3. Microglial activation and neuronal death in CNS neurons of cathepsin D-deficient mice. Neuronal storage of hydrophobic storage materials such as subunit c of mitochondrial F₉F₁-ATP synthase is the primary insult due to cathepsin D-deficiency. The accumulation of these proteolipids facilitate the formation of neuronal ceroid/lipofuscin leading to neuronal dysfunction and damage. Microglia are activated by opposing these storage neurons and/or their own accumulation of proteolipids to produce NO through iNOS. Microglial NO may initiate an intensive inflammatory response in the CNS leading to secondary massive neurodegeneration.
lambs have a severe brain atrophy which is never observed in cathepsin D-deficient mice. These discrepancies may be due to the species difference, the maturity of the CNS, and/or the gestation periods.

3.4. Phenotypes of cathepsin B- and cathepsin L-deficient mice

Cathepsin B-deficient mice show no obvious phenotype (Deussing et al., 1998), but a reduction in premature intrapancreatic trypsinogen activation (Halangk et al., 2000) and increased resistance to TNF-α-mediated hepatocyte apoptosis (Giucciardi et al., 2000) were observed under experimental conditions. Cathepsin L-deficient mice also present with a reduction in CD4+ T cells (Nakagawa et al., 1998) and recurrent hair loss (Roth et al., 2000). More recently, however, it has been reported that combined deficiency of cathepsins B and L is lethal during the second to fourth week of life. These double-mutant mice reveal massive apoptosis of select neurons in the cerebral cortex and the cerebellar Purkinje and granule cell layers resulting in a brain atrophy (Felbor et al., 2002), suggesting that cathepsins B and L are essential for maturation and integrity of the postnatal CNS and that they compensate for each other. In the double-mutant mice, neurodegeneration is preceded by an accumulation of inclusions characterized by electron-dense, often membrane-bound bodies of varying size and shape occasionally containing lamellae. Furthermore, the double-mutant mice show normal activities of both palmitoyl protein thioesterase and tripeptidyl peptidase I, and no clear accumulation of subunit c and ceroid-lipofuscin. Thus, phenotypes of mice deficient for both cathepsins B and L is ultrastructurally and biochemically distinct from those seen in cathepsin D-deficient mice and classical NCLs.

4. Conclusions

Cathepsins are now recognized to have more complex functions than simply being garbage disposers, and their imbalance during aging and age-related diseases may provoke deleterious effects on CNS neurons. The growing understanding of consequences of their age-related changes in neurons and microglia could contribute to the development of therapeutic interventions in massive neurodegeneration associated with age-related diseases such as Alzheimer’s disease and NCLs.

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References


