Review Article Neurobiology

International Journal of Pharma and Bio Sciences

ISSN
0975-6299

CATHEPSIN B: A CONTROVERSIAL TARGET FOR ALZEIHMER'S DISEASE

YADAV M[1] AND AVASTHI A S[*1]

[1]Amity Institute of Biotechnology, Amity University, Noida, UP, India.

ABSTRACT

Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disorder, with unresolved etiology and is characterized by the long latency between the initial dysregulation processes and the late appearance of clinical symptoms. It slowly leads to loss in memory, thinking skills, visuospatial orientation, judgement and personality and eventually the person becomes profoundly mute, disabled and immobile. Amyloid beta (Aβ) generation is the critical initiating event for the development of AD. Cathepsin B (CatB) is an established biomarker for AD. However, its therapeutic role still needs further investigation. Some studies suggest that the CatB act as an anti-amyloidogenic agent via C-terminal degradation of Aβ peptides, and hence CatB inhibition increases Aβ levels and plaque deposition. While other studies suggest that CatB inhibition or knockout reduces Aβ levels and improves memory deficit in AD patients. This review highlights recent studies focussing on the role of CatB in progression or inhibition of AD.

KEY WORDS: *Alzheimer's disease (AD), Cathepsin B (CatB), Aβ aggregates, anti-amyloidogenic, and Amyloid precursor protein (APP)*

AVASTHI A S*

Amity Institute of Biotechnology, Amity University, Noida, UP, India.

Received on: 20.12.2016
Revised and Accepted on: 13-03-2017
DOI: http://dx.doi.org/10.22376/ijpbs.2017.8.2.b369-373

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in older persons, with an increasing incidence as a function of age[1]. The progression of AD is slow but relentless, with symptoms often progressing to more than 10 years. Initial symptoms are forgetfulness and other memory disturbances; with progression of the disease other symptoms such as specific language impairment (SLI), loss of mathematical skills, and loss of learned motor skills appear. In last stages of AD, affected individuals may become incontinent, mute, and unable to walk. The terminal event is usually an intercurrent disease, often pneumonia.The two pathologic hallmarks of AD, particularly evident in the end stages of the illness, are plaques (Aβ aggregates) and tangles (tau aggregates). Amyloid beta (Aβ) generation is the critical initiating event for the development of AD because tau aggregates are formed in other diseases too such as frontotemporal lobar degenerations, progressive supranuclear palsy, and corticobasal degeneration, but Aβ deposits do not ensue. Also, mutations in the gene for tau do not give rise to AD but rather cause frontotemporal lobar degenerations while mutations in Aβ give rise to AD.Amyloid precursor protein (APP) is a cell surface protein with a single transmembrane domain that may function as a receptor, possibly for prion protein (PrPc) among other ligands and consists of Aβ portion of protein that extends from the extracellular region into the transmembrane domain. Processing of APP begins with cleavage in the extracellular domain, followed by an intramembranous cleavage. If APP is first cleaved by α-secretase and then by γ-secretase, a harmless soluble peptide is formed, whereas if APP is first cleaved by β-secretase or β-amyloid-converting enzyme (BACE) and then by γ-secretase, Aβ peptides are formed, which form pathogenic aggregates and contribute to the characteristic plaques of AD. The variation in peptide length arises from alterations in the exact location of the γ-secretase cleavage, resulting in a C-terminal heterogeneity of the resulting peptide population. Hence, numerous different Aβ species exist, with Aβ40 being the most abundant (~80-90%), followed by Aβ42 (~5-10%). The slightly longer forms of Aβ, particularly Aβ42, are more hydrophobic and fibrillogenic, and are the principal species deposited in the brain. Once generated, Aβ is highly prone to aggregation - first into small oligomers (which may be the toxic form responsible for neuronal dysfunction), and eventually into large aggregates and fibrils.

CATHEPSIN B AND ALZHEIMER'S DISEASE

Cathepsin B (CatB) belongs to the class of cysteine proteases and it degrades peptides and proteins that enter the endolysosomal system through endocytosis or phagocytosis[2]. CatB possesses the unique ability to act both as a dipeptidyl carboxypeptidase and an endopeptidase. However, the carboxyldipeptidic activity of CatB is greater than endopeptidic activity due to presence of 20 residue occluding loop containing 2 histidine residues (His 110 and His 111) on its catalytic site.CatB is encoded by the CTSB gene in humans. CTSB gene consists of 13 exons and is located on chromosome 22. CTSB gene promoter region contains a GC-rich sequence including many SP1 sites, which is similar to housekeeping gene. CTSB gene has at least five transcript variants encoding same protein. CatB is synthesized as a preproenzyme of 339 amino acid with a single peptide of 17 amino acids on the rough endoplasmic reticulum. It is then transported to Golgi apparatus and processed into CatB. Mature CatB is composed of a heavy chain (25-26 kDa) and a light chain (5 kDa), which are linked by disulfide bridge. CatB plays an important role in various diseases such as cancer and AD[3-4].In AD brains, neuronal CatB is present in most early endosomes, internalization and processing site of APP to form Aβ[4-5]. CatB is also associated extracellularly with amyloid plaques. CatB also colocalizes with both Aβ40 and Aβ42 in regulated secretory vesicles in chromaffin cells[6]. Although CatB is closely associated with intracellular and extracellular Aβ, the exact function of CatB in APP processing and Aβ metabolism in central nervous system is still controversial. Some studies suggest that CatB might cleave APP and contribute to Aβ generation, leading to neuronal deficits in AD[4-7]. While, some other studies suggest that CatB may catalyse the cleavage of Aβ peptides, resulting in Aβ degradation and neuroprotection[8-14].

ROLE OF CATHEPSIN B IN AMYLOID BETA DEGRADATION: INHIBITOR OF ALZHEIMER'S DISEASE

In 2006, first experimental study supporting the role of CatB in Aβ degradation was conducted by Mueller-Steiner *et al.*[8]. They showed that CatB effectively cleaved Aβ42 peptides resulting in formation of C-terminally truncated Aβ peptides that are less amyloidogenic. Genetic inactivation of CatB in familial AD hAPP mice model increased Aβ formation leading to increase in plaque deposition. CatB expression in aged hAPP mice reduced pre-existing Aβ deposits including thioflavin S-positive plaques. The study showed that CatB possessed anti-amyloidogenic and neuroprotective activities, lack of CatB activity might promote AD and increase in CatB activity could counteract AD neuropathology. In another study conducted by Sun *et al*, it was found that Cystatin C (CysC) acts as a key inhibitor of CatB-dependent Aβ degradation *in vivo*[9]. CysC removal is highly effective in promoting CatB-dependent truncation of Aβ42, the most pathogenic form of Aβ peptides in brain. This was evident from the fact that in CysC – deficient mice, levels of Aβ42 peptides were found to be lower than in the wild-type mice. In hAPP-J20 mice, CatB inhibition of CysC elevated the relative abundance of Aβ42, but this was not evident in CatB deficient mice. Conversely, CatB inhibition in young hAPP-J20 mice elevated the levels of Aβ42, but only when CysC levels were reduced. Hence, the study demonstrated that CysC-CatB interaction modulates the relative abundance of Aβ42 and CysC inhibits the CatB-induced Aβ42 truncation. Therefore, this study showed that CatB inhibitor CysC is a potential target for treating AD and supports the work of Mueller-Steiner *et al* by demonstrating that CatB causes degradation of Aβ peptides[8].In a study conducted by Butler *et al*, it was

found that low concentration of Z-Phe-Aladiazomethylketone (PADK) results in increase in CatB concentration and increase in Aβ degradation[10]. Hence, selective lysosomal modulation by PADK can be a potential strategy for treatment of AD.In another study conducted by Wang *et al*, it was found that increase in CatB activity lowers Aβ deposition, especially Aβ42 deposition, in AD patients regardless of familial mutations[11]. Hence, CatB activity enhancement could be a new potential strategy for AD treatment.In recent study of Moon *et al* for determining the factors responsible for cognitive and neurogenic benefits of running, it was found that running increased levels of CatB in gastrocnemius muscle and plasma of mouse and CatB is an important factor for cognitive and neurogenic benefits of running[12]. Furthermore, brain-derived neurotrophic factor (BDNF) and doublecortin (DCX) expression enhanced by application of recombinant CTSB gene in adult hippocampal progenitor cells through a mechanism dependent on P11 protein. Also, in CTSB knockout mice, adult hippocampal neurogenesis and spatial memory function were not enhanced by running. Similarly, CatB levels were also found to be elevated in plasma of rhesus monkeys and humans after treadmill exercise. In humans, changes in level of CatB correlated with hippocampus-dependent memory function and fitness. Hence, this study suggested that CatB acts as mediator for cognitive and neurogenic benefits of running, further supporting the findings of Mueller-Steiner *et al* focussing on the positive effect of CatB on brain[8].In another study conducted by Pait *et al* for studying protein clearing role of lysosomes, it was demonstrated that Z-Phe-Ala-diazomethylketone (PADK; or Z-FA-DMK) positively modulates lysosomal pathway by CatB upregulation, plaques and tangles reduction, and synaptic decline in transgenic mouse models of both, early onset familial AD as well as AD lacking familial mutations[13]. This study indicated that CatB modulators enhance protein clearance mechanisms to promote synaptic markers recovery and reduce multi-proteinopathy. Hence, this study also supports the findings of Mueller-Steiner *et al* (2006) and shows CatB modulators have potential to slow synaptic decline and associated cognitive deficits in AD[8] .In another recent study by Tiribuzi *et al*, it was demonstrated that transcrocetin, a constituent of *Crocus sativus L.*, upregulates CatB leading to enhancement in degradation of Aβ in AD monocytes[14]. CatB inhibitor CA074Me counteracted transcrocetin-induced effect. Hence, transcrocetin can be another potential drug for the treatment of AD.Thus, all the studies cited above suggest that CatB degrades Aβ peptides, CatB inhibition leads to increase in Aβ formation and CatB expression in AD reduces the level of pre-existing Aβ plaques. CysC inhibits CatB-dependent Aβ truncation and CysC-CatB interaction modulates Aβ levels. Moreover, lysosomal modulator PADK increases CatB concentration leading to increase in Aβ degradation. Also, CatB mediates cognitive and neurogenic benefits of running. Furthermore, CatB modulatory compounds enhance protein clearance mechanisms to promote synaptic markers recovery and reduce multi-proteinopathy. Transcrocetin which upregulates CatB was suggested as a potential drug for AD.

ROLE OF CATHEPSIN B IN AMYLOID BETA FORMATION: PROMOTER OF ALZHEIMER'S DISEASE

There have been many reports where CatB has been investigated for its role as a promoter for Aβ formation ultimately leading to AD. Major source of extracellular Aβ that is responsible for the Aβ aggregation in AD is located in secretory vesicles of neurons. Extracellular Aβ is generated during the β-secretase processing of APP. Previously, the major β-secretase activity was considered to be a cysteine protease. This was proved by a study conducted by Hook *et al.,* in 2005 where they purified the representative cysteine protease and identified it as CatB by peptide sequencing[6]. Colocalization of CatB with Aβ in these vesicles was demonstrated by immunoelectron microscopy. Cysteine protease inhibitor, CA074Me (cell permeable form of CA074) had no effect on Aβ secreted by regulated secretory pathway of chromaffin cells but CA074 reduced extracellular Aβ released by the constitutive pathway. This was the first study demonstrating the role of CatB as β-secretase in regulated secretory pathway of brain neurons and CatB inhibitors as potential drugs to reduce Aβ load in AD.In another study, Hook *et al* demonstrated that cysteine protease inhibitors CA074Me and E64d effectively reduces memory deficit, Aβ plaque load, brain Aβ, and β-secretase activity in London APP mouse model but have no effect in Swedish/London APP mice[15]. This difference is due to the expression of wild type (WT) β-secretase site containing APP in London APP mouse, and Swedish mutant (Swe) β-secretase site containing APP in Swedish/London APP mice. This difference was as expected as RSV β-secretase and CatB assays used for compound selection identifies only those compound which inhibits WT β-secretase substrate cleavage and not Swe β-secretase substrate cleavage. Cysteine protease inhibitors may act by inhibiting CatB in London APP mice, thus reducing the Aβ peptides. Since APP containing WT β-secretase site is expressed in most of the AD patients, efficacy in London APP mouse expressing APP containing WT β-secretase site demonstrates the cysteine protease inhibitors potential as therapeutic agents for AD. Therefore, this study showed that CatB inhibition by cysteine protease inhibitors CA074Me and E64d reduces Aβ load in AD.In further study, Hook *et al* demonstrated that CTSB gene knockout reduces Aβ40 and Aβ42 by up to ~67%, reduces CTFβ by 41% and increases sAPPα by 61% in mice expressing hAPPwt[16]. This shows that CatB has major role in Aβ peptides formation from hAPPwt in brain. As most AD patients express hAPPwt, this data validates the usage of CatB as potential target for development of inhibitors to reduce Aβ deposits in AD.Hook *et al* in 2010 also demonstrated the pharmacogenetic differences in effects of CatB inhibitors in different mice models[17]. CatB inhibitors were found to have no effect in mice expressing APP containing rare Swe β-secretase site. CatB knockout decreased Aβ deposits in mice expressing WT APP. Hence, difference in CatB inhibitors responses in different AD mice model is due to the specificity of CatB to cleave WT β-secretase site of APP for Aβ formation and not the Swe mutant β-secretase site. In contrast, BACE1 β-secretase

cleaves Swe mutant site. BACE1 data do not preclude CatB as also being a β-secretase. It suggests that CatB and BACE1 may jointly act as β-secretases. Significantly, most of AD patients express WT APP and, therefore, CatB inhibitors represent potential drugs for AD.In another study conducted by Sundelof *et al* for CatB levels in plasma and CSF samples in persons with AD, mild cognitive impairment (MCI), and healthy controls, it was found that plasma CatB levels were higher in AD patients compared to healthy controls[18]. However, no such significant increase was seen in CatB levels in CSF. No suitable possible mechanism could be provided. This study corroborated the findings of Hook *et al*.[6,15-17]. Hence, further investigation is needed to confirm the role of CatB as target of AD.Further studies by Hook *et al.,* it was found that E64d (CatB inhibitor) reduced Aβ deposits, C-terminal β-secretase fragment (CTFβ), and CatB activity but increased BACE1 activity in brain of AD guinea pigs and mice models expressing APP containing WT β-secretase site[19]. Thus, E64d reduces Aβ deposits by inhibiting CatB and not BACE1 activity.In another study conducted by Kindy *et al* (2012), it was found that deletion of the CatB gene improves memory deficits in the AβPPWT/Lon AD mouse model expressing human AβPP containing the WT β-secretase site sequence that is present in most AD patients[20]. However, BACE1 gene knockout had no effect on APPWT/Lon mice. The study supports the findings of Hook *et al* and further provides evidence for the possibility of CatB as drug target for improving memory deficits in most AD patients. Pyroglutamate Aβ peptides (pGlu-Aβ) are pernicious forms of Aβ peptides and are N-terminally truncated forms of full length Aβ peptides (flAβ) in which N-terminal glutamate is cyclized to pyroglutamate. flAβ are formed by both β-secretase (BACE1) and CatB cleavage but it is still unknown whether cleavage by BACE1 or CatB can form pGlu-Aβ. Therefore, Hook *et al* also examined effects of CTSB and BACE1 gene knockout on pGlu-Aβ levels in transgenic APP/Lon mice containing WT β-secretase activity[21]. CTSB knockout or overexpression reduced or increased, respectively, pGlu-Aβ and flAβ deposits, but BACE1 gene knockout had no effect. CatB inhibitors, E64d and CA074Me, also reduced pGlu-Aβ and flAβ plaque load. Hence, this study illustrate that CatB has role in pGlu-Aβ and flAβ formation in development of AD.Weber *et al* synthesized monoclonal antibodies against CatB to clarify the role of CatB in neurodegeneration, and it was found that CatB antibodies has 5 different binding sites, thus giving the opportunity to improve detection of CatB by combining CatB specific antibodies in oligoclonal antibody mixtures[22]. This may result in improved detection of CatB, an established biomarker for AD.In recent study conducted by Jeon *et al*, it was demonstrated that chalcone derivatives compounds 7 and 11 reduced tau phosphorylation, insoluble Aβ peptide formation and p25 formation by inhibiting both μ-calpain and CatB enzymes[23]. Hence, Chalcone derivatives compounds 7 and 11 can also be a potential drug for treating AD by inhibition of CatB.In another recent study conducted by Na *et al*, it was proved that Aβ42 upregulates CysLT1R and CatB and that CatB is induced by CysLT1R activation[24]. The study also demonstrated that 6-shogaol, a compound present in ginger, inhibits CysLT1R leading to downregulation of CatB and reduction in Aβ deposition. Therefore, this study also supports Hook *et al* findings and proves CatB as potential target for AD and 6-shogaol, a CysLT1R/CatB inhibitor, is a novel potential drug to treat AD. Hence, these studies demonstate that CatB inhibition and CTSB gene knockout leads to improvement in memory deficits and reduction in flAβ and pGlu-Aβ peptides deposits. Differences in CatB inhibitors effects on different AD mice models are due to specificity of CatB to cleave APP at WT β-secretase site and not on Swe β-secretase site, which are cleaved by BACE1. Hence, CatB is a potential target for AD and CatB inhibitors can prove to become potential drugs for AD treatment.

CONCLUSION

In various studies conducted on AD, CatB has been demonstrated to act as an anti-amyloidogenic agent via C-terminal degradation of Aβ peptides (including both Aβ40 and Aβ42). Furthermore, it was also found that CatB inhibition increases Aβ levels and plaque deposition. CatB cleaved both fibrillar as well as nonfibrillar assemblies of Aβ peptides into shorter Aβ peptides that are less pathogenic and amyloidogenic. Moreover, CysC had been suggested to be the main inhibitor of anti-amyloidogenic action of CatB. Also, recent studies conducted in 2016 by various research groups have showed that the CatB levels are increased during running and lead to enhanced hippocampus-dependent memory function. CatB modulators enhance protein clearance mechanisms to promote synaptic markers recovery and thus reduce multi-proteinopathy. Transcrocetin which causes upregulation of CatB may be suggested as a potential drug for AD.In contrast, some other studies suggested that CatB inhibition by gene knockout, chemical inhibitors or RNA silencing can lead to reduction in Aβ deposits and thus improve memory deficits in AD. Furthermore, it was shown that plasma CatB levels were higher in AD patients as compared to healthy persons. Moreover, recently in 2016, CatB inhibitors Chalcone derivatives compounds 7 and 11 and ginger compound 6-shogaol were also proposed to be potential drugs for treating AD. Based on these data it has been hypothesised that inhibition or knockout of CatB may be a therapeutic strategy in AD.Thus, even in 2016, CatB role in AD is still controversial. It still remains unclear if CatB is promoting or suppressing AD pathogenesis. Hence, further investigation of CatB as a therapeutic protein for AD is warranted.

CONFLICT OF INTEREST

Conflict of interest declared none.

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Reviewers of this article

Dr. Navkiran kans, Ph.D.

Assistant Professor, Amity Institute of Biotechnology, Amity University, Noida, India

Asst.Prof.Dr. Sujata Bhattacharya

Assistant Professor, School of Biological and Environmental Sciences, Shoolini University, Solan (HP)-173212, India

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International Journal of Pharma and Bio sciences.

We sincerely thank the above reviewers for peer reviewing the manuscript