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REVIEW ARTICLE

Amyloid beta peptide-degrading microbial enzymes and its implication in drug design

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Abstract

Alzheimer's disease (AD) is a chronic and progressive neurological brain disorder. AD pathophysiology is mainly represented by formation of neuritic plaques and neurofibrillary tangles (NFTs). Neuritic plaques are made up of amyloid beta (Aβ) peptides, which play a central role in AD pathogenesis. In AD brain, Aβ peptide accumulates due to overproduction, insufficient clearance and defective proteolytic degradation. The degradation and cleavage mechanism of Aβ peptides by several human enzymes have been discussed previously. In the mean time, numerous experimental and bioinformatics reports indicated the significance of microbial enzymes having potential to degrade Aβ peptides. Thus, there is a need to shift the focus toward the substrate specificity and structure–function relationship of Aβ peptide-degrading microbial enzymes. Hence, in this review, we discussed in vitro and in silico studies of microbial enzymes viz. cysteine protease and zinc metallopeptidases having ability to degrade Aβ peptides. In silico study showed that cysteine protease can cleave Aβ peptide between Lys16–Cys17; similarly, several other enzymes also showed capability to degrade Aβ peptide at different sites. Thus, this review paves the way to explore the role of microbial enzymes in Aβ peptide degradation and to design new lead compounds for AD treatment.

Keywords Alzheimer's disease · Amyloid β-peptide · Aβ-degrading enzymes · Molecular modeling

Introduction

Alzheimer's disease (AD) is a neurological disorder of brain. It has been reported in the year 2000 that nearly 25 million people were affected worldwide by AD and this number would reach up to 63 and 114 millions by 2030 and 2050, respectively (Loncarevic et al. 2005). Because of this, AD is a serious problem in terms of medical and financial views to the society. There are different hypotheses in AD, including cholinergic, amyloid cascade, tau, oxidative imbalance and mild cognitive impairment (Schneider et al. 2011; Love et al. 2009; Ballard et al. 2011; Hardy and Selkoe 2002; Glenner and Wong 1984). The hypotheses, concepts and theories regarding AD have been discussed in earlier review (Barage and Sonawane 2015). In the cholinergic hypothesis, shortage of neurotransmitters like acetylcholine and butyrylcholine have been identified (Schneider et al. 2011). Therefore, inhibition of enzymes such as acetylcholinesterase (AChE), butyrylcholinesterase (BChE) which are responsible to break down acetylcholine and butyrylcholine has been considered as a standard approach to minimize symptomatic effects of AD (Schneider et al. 2011). The synthesis and molecular docking studies revealed potential of 2-substituted benzimidazoles as an acetyl cholinesterase inhibitor (AChE) (Sonawane et al. 2018).

Another hypothesis is the amyloid cascade, in which amyloid plaques are formed by accumulated Aβ peptides in AD patient's brains (Reitz 2012; Barage et al. 2015). The amyloid plaque containing Aβ peptides is the pathological hallmark of AD (Hardy and Selkoe 2002; Glenner and Wong 1984). The $A\beta_{1-42}$ peptides are main constituents of amyloid plaques in AD (Gouras et al. 1998; Masters et al. 1985; Tanzi and Bartman 2005). The Aβ peptide is produced after the sequential cleavage of amyloid precursor protein (APP) by beta- and gamma-secretases in the amyloidogenic pathway. The inhibition of these secretases becomes another approach in AD treatment (Love et al. 2009; Ballard et al. 2011). The steady-state concentration of Aβ peptide is tightly controlled by Aβ-degrading proteolytic enzymes

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and perivascular drainage (Weller et al. 2002; Nalivaeva et al. 2008; Hawkes et al. 2011). It has been showed that the arginine containing short peptide, RR-AFC can destabilize and inhibit the aggregation of Aβ protofibril by hydrogen bonding and hydrophobic interactions (Barale et al. 2019). There are various enzymes involved in Aβ peptide clearance such as insulin-degrading enzyme (IDE), neprilysin (NEP), endothelin-converting enzyme (ECE), angiotensin-converting enzyme (ACE), matrix metalloproteinases (MMPs) and plasmin (Iwata et al. 2001; Qiu et al. 1998; Tucker et al. 2000; Yin et al. 2006; Zou et al. 2007; Cimerman et al. 1999). Therefore, these enzymes can be targeted to reduce the Aβ peptide load in the AD brain. In addition, several in vitro and in silico studies reported the potential of microbial enzymes to degrade Aβ peptides (Hsu et al. 2009; Yoo et al. 2010; Dhanavade et al. 2013; Dhanavade and Sonawane 2014; Jalkute et al. 2015).

Earlier studies suggested that Nattokinase enzyme from *Bacillus subtilis* Natto (Hsu et al. 2009) and aminopeptidase from *Streptomyces griseus* KK565 can degrade Aβ peptides (Yoo et al. 2010). Similarly, experimental and some computational work revealed the role of microbial enzymes viz. aminopeptidase from *Streptomyces griseus* KK565, cysteine protease from *Xanthomonas campestris* and gelatinase from *Enterococcus faecalis* in Aβ peptides' degradation (Yoo et al. 2010; Dhanavade et al. 2013; Dhanavade and Sonawane 2014; Jalkute et al. 2015). Thus, computational studies of microbial enzymes could be useful to understand Aβ peptide degradation in detail at the atomic level (Dhanavade et al. 2013; Dhanavade and Sonawane 2014; Jalkute et al. 2015). In this review article, we have summarized certain bacterial enzymes having potential to degrade Aβ peptides, which would be useful to design new therapeutic strategies to control Aβ peptides.

Microbial infections and Alzheimer's disease

Several microorganisms such as bacteria, viruses and yeasts have been suspected in AD brains and the oral infections were found to be responsible for the etiology of late onset of AD (LOAD) (Riviere et al. 2002; Poole et al. 2013) (Table 1). Numerous pathogens' chronic periodontitis like *P. gingivalis*, *T. forsythia*, and *T. denticola* have been implicated in the development of several inflammatory diseases, out of which *T. denticola* represents a spirochete which mainly occurs in the AD brain (Riviere et al. 2002; Poole et al. 2013). The pathogenic bacteria like *Chlamydophila pneumonia* are likely to cause infection and cause pathogenesis in AD (Honjo et al. 2009; Maheshwari and Eslick 2015; Shima et al. 2010). Similarly, the role of bacterium such as *H. pylori* (monoinfection) has also been found in AD (Honjo et al. 2009). It was also observed that *T. pallidum* causes brain atrophy and deposition of Aβ in the atrophic form of general paresis (Miklossy 2011a, b). Also, the herpes simplex virus (HSV-1) is associated with amyloid-containing plaques and/or NFTs found to be involved in AD pathology (Harris and Harris 2018). Similarly, several studies have also been reported to reveal the association between Aβ accumulation in the brain and HSV infection (De Chiara et al. 2010; Itzhaki et al. 2008). Hence, understanding these microbial infections and pathogenesis could be an important task to control the adverse effects of AD.

Table 1 The bacteria present in brain which can impact on AD

Sr. no.	Name of bacteria which can influence in AD brain	References
1	*Escherichia coli*	Zhan et al. (2016)
2	*Chlamydia pneumoniae*	Balin et al. (2018)
3	*Helicobacter pylori*	Kountouras et al. (2009)
4	*Lactobacillus fermentum*	Wang et al. (2015)
5	*Bacteroides fragilis*	Lukiw (2016)
6	*Klebsiella pneumonia*	Bieler et al. (2005)
7	*Mycobacterium tuberculosis*	Alteri et al. (2007)
8	*Salmonella typhimurium*	Castelijn et al. (2012)
9	*Salmonella enterica*	Solomon et al. (2005)
10	*Bacillus subtilis*	Romero et al. (2014)
11	*Pseudomonas*	Dueholm et al. (2010)
12	*Streptococcus mutans*	Oli et al. (2012)
13	*Candida albicans*	Garcia et al. (2013)

Gut-microbiota and Alzheimer's disease

Haran and co-workers have found that the microbiome of AD patients is associated with the disregulation of the anti-inflammatory p-glycoprotein pathway (Haran et al. 2019). Their conclusions are based on functional studies combined with machine learning approaches (Haran et al. 2019). It has been reported that the gut bacteria can produce amino acids like gamma-amino butyric acid (GABA), tryptophan and monoamines such as serotonin, histamine, dopamine, which play an important role in the brain (Briguglio et al. 2018; Lyte et al. 2018; Thomas et al. 2012; Wall et al. 2014). The relationship between gut microbiota and brain of the respective person has been discussed elegantly (Giau et al. 2018a, b). It has been showed that the commensal intestinal flora helps the host to produce necessary vitamins (Nishino et al. 2013). Borghammera and Beege hypothesized that the disease starts in the gut and then further spread to the brain (Borghammera and Berge 2019). The gut-related inflammation proves systematic inflammation, neuro-inflammation and endotoxemia, which has resulted into the development of neural disorders and psychiatric illness in later life (Sochocka et al. 2019). The amino acids produced by gut microbiota serves as a component of neurotransmitters

influencing neurons in central nervous system (CNS) (Lyte et al. 2018). Pro-inflammatory cytokines and deposited Aβ peptides create positive feedback in the development of neurodegenerative diseases. Hence, there are considerable evidences which revealed that gut microbiota affect CNS, neuroinflammation and neurodegenerative disease such as AD (Sochocka et al. 2019). Hence, Giau and co-workers highlighted that cell signaling study might be useful to understand the role of different components produced by gut microbiota in AD (Giau et al. 2018a, b).

Human enzymes involved in Aβ peptide degradation and clearance

There are several drugs which can reduce Aβ peptides production, but they have been reported with certain side effects (Henley et al. 2009; Bateman et al. 2009). Some anti-dementia and memory-impairing drugs like nicotinic antagonist, mecamylamine, and the *N*-methyl-D-aspartic acid (NMDA) receptor antagonist, MK-801, have been described (Yuedea et al. 2007). Hence, research should also be focused on reducing the Aβ peptide levels by means of alternative approaches. In near future, enzymatic degradation can be mainly targeted to reduce the Aβ peptide levels and AD risk (Baranello et al. 2015). In human brain, there are many proteases or peptidases, which showed capability to degrade Aβ either in vitro or in vivo as can be seen in Fig. 1. These enzymes include neprilysin (NEP) (Iwata et al. 2001), endothelin-converting enzyme (ECE)-1 (Eckman et al. 2001), insulin-degrading enzyme (IDE) (Kurochkin and Goto 1994; McDermott and Gibson 1997; Qiu et al. 1998), angiotensin-converting enzyme (ACE) (Hu et al. 2001), uPA/tPA–plasmin system (Sasaki et al. 1988; Verde et al. 1988), cathepsin D (Yamada et al. 1995a, b; Hamazaki 1996), gelatinase A (Yamada et al. 1995a, b), gelatinase B (Backstrom et al. 1996), aminopeptidase A (Sevalle et al. 2009), cathepsin B (Mueller-Steiner et al. 2006), antibody light chain c23.5, hk14 (Rangan et al. 2003), and α2-macroglobulin complexes (Qiu et al. 1996). Many of these enzymes possess more than one cleavage sites in Aβ peptide (Fig. 1, Table 2). Therefore, up-regulation of these proteases in the brain could be a possible way to control accumulation and Aβ peptides' aggregation, which could prove as an effective therapeutic strategy (Mueller-Steiner et al. 2006; Rangan et al. 2003; Qiu et al. 1996; Leissring et al. 2003). However, cross-reactivity of these enzymes could be another issue. Although these enzymes in human brain decrease the load of Aβ peptides, but the factors such as enzymatic loss through genetic mutations or non-genetic reasons like direct oxidative damage or enhanced production

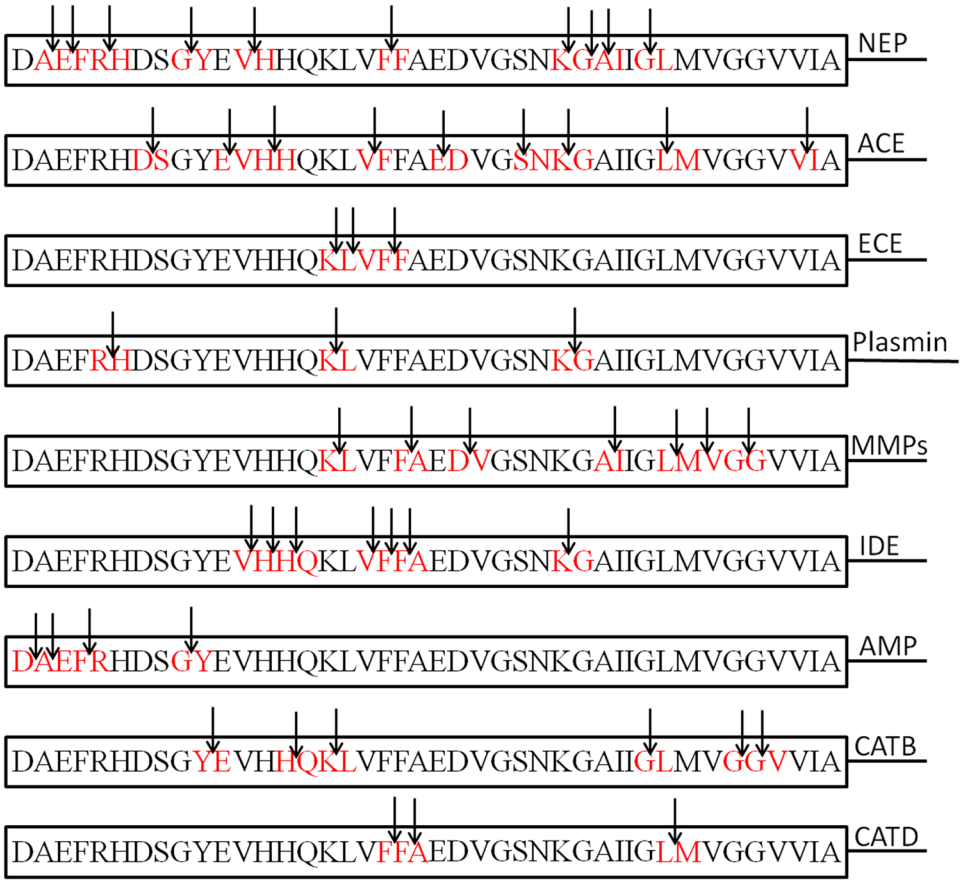

Fig. 1 Cleavage sites of amyloid beta (Aβ) peptide for human, microbial enzymes

Table 2 The amyloid beta (Aβ) peptide degrading microbial, human enzymes and their cleavage sites

Enzymes	Amyloid beta (Aβ) peptide cleavage site	References
Neprilysin (NEP)	A2–E3, E3–F4, R5–H6, G9–Y10, V12–H13, F19–F20, K28–G29, G29–A30, A30–I31 and G33–L34	Howell et al. (1995); Nalivaeva et al. (2011)
Angiotensin-converting enzyme (ACE)	D7–S8, E11–V12, H13–H14, V18–F19, E22–D23, S26–N27, K28–G29, L34–M35 and V40–I41	Zou et al. (2009); Hu et al. (2001)
Endothelin-converting enzyme (ECE)	K16–L17, L17–V18, F19–F20	Eckman et al. (2001); Schulz et al. (2009); Sonawane and Barage (2015)
Plasmin	R5–H6, K16–L17, K28–G29	Werb (1997); Ledesma et al. (2000)
Matrix metalloproteiases (MMPs)	K16–L17, F20–A21, D23–V24, A30–I31, L34–M35, M35–V36, G37–G38	Carvalho et al. (1997); Yan et al. (2006)
Insulin degrading enzyme (IDE)	V12–H13, H13–H14, H14–Q15, V18–F19, F19–F20, F20–A21, K28–G29	Farris et al. (2003)
Aminopeptidase (AMP)	D1–A2, A2–E3, F4–R5, G9–Y10	Sevalle et al. (2009)
Cathepsin B (CATB)	Y10–E11, H14–Q15, K16–L17, G33–L34, G37–G38, G38–V39	Mueller-Steiner et al. (2006)
Cathepsin D (CATD)	F19–F20, F20–A21, L34–M35	Rogeberg et al. (2014); Sadik et al. (1999)

of inhibitors may result into abnormal Aβ catabolism (Wang et al. 2006). Because of these limitations, there is a need to discover new Aβ-degrading enzymes from other sources as well to study Aβ catabolism in detail at the molecular level. There are different enzymes from microbial sources having ability to degrade Aβ peptides. Further, these microbial enzymes can be studied to design novel drugs against AD. The enhanced activity of Aβ peptide-degrading enzymes could be a promising approach in AD treatment (Fig. 2).

Microbial enzymes having role in Aβ peptide degradation similar to human enzymes

Several in vitro studies have confirmed the Aβ peptide-degrading abilities of enzymes from microbial sources (Hsu et al. 2009; Yoo et al. 2010; Ningthoujama et al. 2019). Out of which, one report suggests that soluble Keratinase 1 reconstituted on neutral/cationic liposomes can degrade Aβ fibrils efficiently (Ningthoujama et al. 2019); an interesting report on small peptides having ability to inhibit oligomerization/aggregation of Aβ peptides and convert it into non-toxic oligomeric forms (Ribaric 2018). Such type of small peptides could be studied further for their potential role in AD treatment. There is one report in which authors pointed out strong connection between the general mitochondrial dysfunction and AD progression; they discussed how these two processes are interrelated (Giau et al. 2018a, b). Therefore, experimental and computational studies of Aβ peptide-degrading enzymes from microbial sources could be helpful to understand the Aβ peptide cleavage process in detail at molecular level. Sequence analysis, homology modeling, molecular docking and MD simulation studies of cysteine protease from *Xantomonas campestris* showed homology and Aβ peptide cleavage sites similar to human cathepsin B enzyme (Dhanavade et. al. 2013).

Matrix metalloproteinase (MMPs)

Matrix metalloproteinases (MMPs) are zinc and calcium-dependent endopeptidases produced by neuron and glial cells in humans (Yan et al. 2006). The experimental studies performed by Yan and coworkers confirmed that MMP-9 has ability to cleave Aβ peptide (Yan et al. 2006). The important ability of MMP9 over other Aβ-degrading enzymes is to degrade fibrillar Aβ peptides (Backstrom et al. 1996). The elevated activities of MMP-2 and MMP-9 were observed in the hippocampus tissue from AD patient's brain. However, MMP-2, MMP-3 and MMP-9 expression has been found up-regulated in several brain tissues in response to Aβ stimulation (Deb et al. 1996; Miners et al. 2008; Gottschall et al. 1996). The MMP-2 is also known as gelatinase A or type IV collagenase (Roher et al. 1994). The studies done by Roher and coworker showed that MMP-2 cleaves peptide bonds of $A\beta_{1-40}$ and $A\beta_{1-42}$ in between different residues such as Ly16-Leu17, Leu34-Met35 and Met35-Val36 (Gottschall et al. 1996). Backstrom and co-workers determined that MMP-9 is present in the vicinity of extracellular amyloid plaques (Backstrom et al. 1996). Further, it has been confirmed that MMP-9 can also cleave aggregated Aβ fibrils (Gottschall et al. 1996). MMP-9 cleaves Aβ peptides predominantly in between Leu34-Met35 of membrane-spanning domain along with other numerous sites (Backstrom et al. 1996; Jung et al. 2003). The studies showed that MMP2 knock-out has been resulted into increasing $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in the soluble fraction of hippocampus and cortex

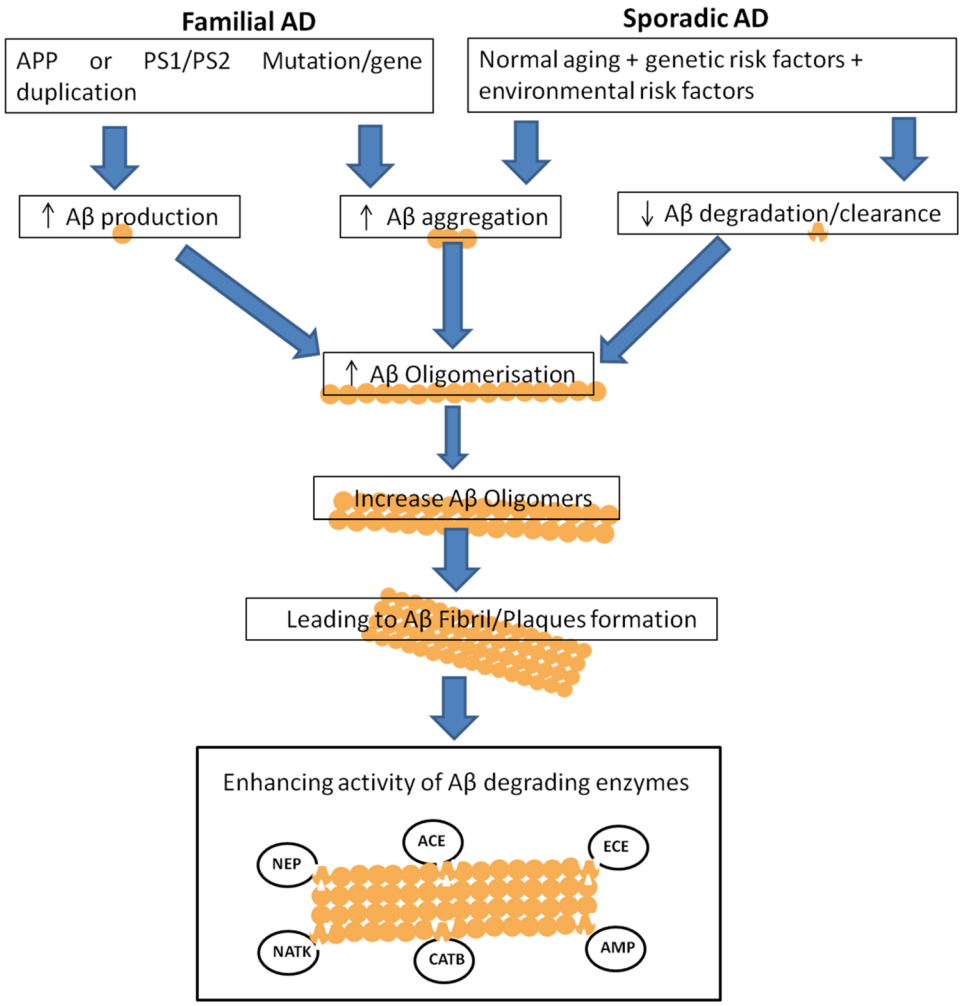

Fig. 2 Aβ peptide production and its clearance by enhance enzymatic activity (↑ increase, ↓ decrease)

(Yin et al. 2006). Also, the increased Aβ peptide levels in the brain were observed after infusion of a broad spectrum metalloproteinase inhibitor suggesting the importance of MMP-2 and other metalloproteinases in Aβ turnover to maintain the steady-state level (Yin et al. 2006).

Therefore, these metalloproteinase from human and other sources can be targeted to study the degradation of Aβ peptide. The X-ray crystal structure of MMP-9 (resolution—2.3 Å) has been solved by Rowsell and group members (Rowsell et al. 2002). The molecular modeling study depicted the potential of gelatinase from *Enterococcus faecalis* to degrade Aβ peptide (Jalkute et al. 2015). This study showed that the active site residue Glu328 of gelatinase from *Enterococcus faecalis* involved in catalytic mechanism by serving as a proton shuttle to cleave peptide bond in between Leu34-Meth35 of wild-type Aβ peptide (Jalkute et al. 2015). Thus, gelatinase from *Enterococcus faecalis* could also be a good target to study the exact cleavage mechanism of Aβ peptide degradation and to design new therapeutic approaches for the treatment of AD.

Cathepsin B (Catb)

The use of cysteine protease to degrade Aβ peptide in vivo has been shown pharmacologically (Frautschy et al. 1998). Further, in vivo study performed by Mueller-Steiner and co-workers also revealed the potential of CatB, a cysteine protease in degradation of Aβ peptide (Mueller-Steiner et al. 2006). Similarly, the role of CatB has also been shown in protein degradation, mainly Aβ peptides (Glabe 2001). However, in certain pathological conditions CatB is secreted by exocytosis (Cataldo and Nixon 1990; Cataldo et al. 1997). In AD, CatB has been found in the extracellular amyloid plaques (Maruyama et al. 2005). It is well known that CatB can also perform processing of APP and Aβ peptides (Cataldo and Nixon 1990; Cataldo et al. 1997). CatB cleaves Aβ peptides from carboxy terminus resulted into reduced $A\beta_{1-42}$ peptides' concentration (Cataldo et al. 1997). Although CatB can efficiently reduce the oligomeric $A\beta_{1-42}$ levels in vitro, it is not known whether the over-expressed CatB also reduces toxic Aβ oligomers level in vivo. CatB can directly reduce the local monomeric and oligomeric $A\beta_{1-42}$ peptide

concentration through proteolytic cleavage (Cataldo et al. 1997). These studies showed that stimulating CatB activity might reduce Aβ peptides level, mainly $A\beta_{1-42}$, resulted into the protection from AD-related deficits. The cystatin C is a cysteine protease inhibitor, which inhibits CatB activity (Cimerman et al. 1999; Turk et al. 1995). The increased CatB activity is achieved by reducing cystatin C levels (CysC, CST3) (Cimerman et al. 1999; Turk et al. 1995). Hence, from these studies it is confirmed that CatB degrades Aβ peptide and could be a possible target for AD treatment.

Bioinformatics study has been performed to find out microbial enzymes having ability to degrade Aβ peptide similar to human CatB (Dhanavade et al. 2013). Molecular docking study performed using AutoDock (Morris et al. 2009) showed that cysteine protease from *Xanthomonas campestris* possesses sequence similarity to human CatB (Dhanavade et al. 2013). The molecular docking and molecular dynamic simulation studies showed that the sulfhydryl hydrogen atom of Cys17 residue of cysteine protease from *Xanthomonas campestris* interacts with carboxylic oxygen of Lys16 of Aβ peptide, indicating the cleavage site (Dhanavade et al. 2013). In this study, three-dimensional fold of cysteine protease from *Xanthomonas campestris* found similar to crystal structure of human CatB (Dhanavade et al. 2013). This study may be helpful to understand Aβ peptide degradation and further, to design new therapeutic approaches for AD treatment (Dhanavade et al. 2013).

Aminopeptidase (Amp)

Aminopeptidases (AMP) (EC 3.4.11.-) are a heterogeneous group of exopeptidases, which catalyzes amino acid removal from the N-terminus of substrates such as proteins or peptides (Taylor et al. 1993a, b; Yao and Cohen 1999). These aminopeptidase enzymes are widely distributed in animal and plant kingdoms. Aminopeptidases are known to play important roles in activation, modulation, and degradation of bioactive peptides (Lendeckel et al. 2000; Stoltze et al. 2000; Hui 2007). The studies done by Sevalle and co-workers confirm that aminopeptidase A (APA) carries out Aβ peptide truncation at N-terminal (Sevalle et al. 2009). It has been noted that the N-terminal truncated Aβ peptide with first two residues deleted and glutamate at position 3 undergoes cyclization (Stoltze et al. 2000; Hui 2007; Saido 1996; Russo et al. 1997). The study performed by Medeiros and co-workers showed that aminopeptidase also plays an important role in tauopathies (Medeiros et al. 2011). Many neurodegenerative disorders are caused due to accumulation of hyperphosphorylated TAU proteins which can form neurofibrillary tangles (Wang et al. 2010; Ballatore et al. 2007). Therefore, the reduction of TAU helps to develop potential therapy for AD and other tauopathies (Bruden et al. 2009). It has been showed by Yoo and co-workers that aminopeptidase from *Streptomyces griseus* KK565 degrades Aβ peptide in vitro (Yoo et al. 2010). Therefore, such microbial enzymes may be targeted to understand the Aβ peptide degradation mechanism.

In silico experiments such as sequence analysis, homology modeling, molecular docking and molecular dynamics simulations have been found useful to understand the exact role of aminopeptidase from *Streptomyces griseus* KK565 in Aβ peptide degradation (Dhanavade and Sonawane 2014). The mutant Aβ peptide was compared with wild-type Aβ peptide, in which aminopeptidase enzyme showed more interactions with wild-type Aβ peptide than mutant Aβ peptide (Fede et al. 2009; Dhanavade and Sonawane 2014). Thus, these experimental and computational studies of aminopeptidase from *Streptomyces griseus* KK565 would be important to understand the Aβ peptide degradation process in detail at the molecular level.

Nattokinase

The experimental study performed by Hsu and coworkers suggest that Nattokinase enzyme from *Bacillus subtilis* Natto has potential to degrade Aβ peptide (Hsu et al. 2009). The bacterial strain *Bacillus subtilis* was isolated from fermented food Natto. Then, the Nattokinase enzyme was purified from this isolated *Bacillus subtilis* strain and further tested to know its ability to degrade Aβ peptide (Hsu et al. 2009). The nattokinase enzyme was found stable at 50 °C; which showed good activity at neutral pH. Therefore, Nattokinase enzyme could be a good target in the drug development studies. Further, exact Aβ peptide degradation mechanism by Nattokinase can be studied in detail at the atomic level using bioinformatics approaches.

Currently, AD treatment has been focused on cholinesterase inhibitors (minimizing symptomatic AD effects) and NMDA-receptor antagonists (Parsons et al. 2013). Many compounds have been tested to minimize the symptomatic effects of AD. The main concern is that only few of these compounds have been appeared in the drug development process or clinical testing by randomized clinical trials. Generally, negative results are reported for these clinical trials (Aprahamian et al. 2013). In last decade, most of the drugs were in phase 3 trials and all of them have failed to provide good clinical benefits, or were suspended because of having severe adverse side effects (Aprahamian et al. 2013). It has been demonstrated that the memantine nanoparticles are more effective than the free drug; hence, MEM–PEG–PLGA nanoparticles (NPs) could be an effective alternative for AD patients (Sanchez-Lopez et al. 2018). Moreover, all drugs currently in clinical trials for AD treatment available in the database of Clinicaltrials.gov till February 12, 2019 have

been reviewed thoroughly (Cummings et al. 2019). Therefore, there is a need to find new targets and approaches in AD treatment. Hence, above-discussed microbial enzymes having potential to degrade Aβ peptides could be an interesting topic for the development of new approaches in AD treatments.

Microbial enzymes and drug discovery in Alzheimer's disease

Earlier in vitro report revealed that stimulating the activity of Aβ-degrading enzymes using potent pharmacological agents could prevent the Aβ pathology (Kuruppua et al. 2016). It is well known that the pathways for Aβ synthesis and degradation have become crucial targets to develop effective treatment for AD. The recent report suggests that Aβ degradation is being used as a more effective strategy than preventing Aβ production (Sikanyika et al. 2019). Hence, Aβ-degrading enzymes are mainly targeted as an effective therapeutic agent in AD treatment (Sikanyika et al. 2019). One report suggests that people with coronary artery disease (CAD) are more prone to develop AD than those without CAD (De la Torre et al. 2004). It is believed that $A\beta_{1-40}$ and APP are having an important role in atherothrombosis, vascular inflammation, vascular and cardiac aging; hence, $A\beta_{1-40}$ can also be considered as a new biomarker for risk stratification in cardiovascular disease (Stakos et al. 2020).

It is quite difficult to isolate human enzymes from AD brain to study degradation mechanism of Aβ peptides. However, microbial enzymes having Aβ peptide-degrading ability can be easily isolated, identified from known microbial species and studied further (Hsu et al. 2009; Yoo et al. 2010; Dhanavade et al., 2013; Dhanavade and Sonawane, 2014; Jalkute et. al. 2015). Hence, these microbial enzymes having ability to degrade Aβ peptide can be further purified to fetch three-dimensional structural information, which could be useful to understand mechanism of Aβ peptide degradation. This experimental and structural information of microbial enzymes could be useful to find out effective drug molecules against the target. These drug molecules can be further tested on human enzymes having maximum sequence similarity with microbial enzymes.

Conclusion

In the current review, we discussed in vitro and in silico studies of microbial enzymes having potential to degrade Aβ peptides similar to human enzymes. These studies could be helpful to understand Aβ peptide degradation in detail at the atomic level. Such microbial enzymes having ability to degrade Aβ peptide at multiple sites may be targeted in the future drug-discovery process to design new therapeutic approaches for AD treatment. Thus, the present review would be helpful to get some useful information about the microbial enzymes involved in Aβ peptide degradation. Further, there is a need to find new enzymes having ability to degrade Aβ peptides from novel microbial sources, which could be useful to understand proper interactions between enzymes and Aβ peptide at molecular level.

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Compliance with ethical standards

Conflict of interest Authors have no conflict of interest.

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