Caspases: A Potential Therapeutic Targets in the Treatment of Alzheimer's Disease

Kuladip Jana*, Bhaswati Banerjee and Pravat Kumar Parida

Division of Molecular Medicine, Bose Institute, Centenary Campus, P 1/12, Calcutta Improvement Trust Scheme VIIM, Kolkata-700 054, India

Abstract

An enormous body of evidence supports the activation of caspases may be responsible for the neurodegeneration associated with Alzheimer's disease (AD) and for that reason, caspases are potential therapeutic targets for the management of this disorder. However, till date, the studies testing with prospective role of caspase inhibitors for the treatment of AD have yet to be realized. Obviously, this is due to the potential side effects due to long term use of caspase inhibitors. In addition, a further assessment is warned in relation to the therapeutic efficacy and stress of targeting caspase inhibition with the potential caspase inhibitors and its improved delivery system to the brain in the treatment of AD.

Keywords: Alzheimer's disease; Caspases; Neurofibrillary tangles; Long term depression; Long term potentiation

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by extensive neuronal loss leading to confusion, disturbances in short term memory, cognitive impairment and dementia [1-3]. AD is diagnosed based on the extent of senile plaques composed of beta-amyloid (Aβ) and neurofibrillary tangles (NFTs) along with neuron loss [1,2]. NFTs consist of Paired Helical Filaments (PHF) resulting from the hyper-phosphorylation of the microtubule-binding protein tau. Tau plays an essential role in maintaining microtubule stability and in AD, neuronal tau is strangely phosphorylated and proteolyzed resulting in an impairment of the normal functions of tau [1-3]. In addition to NFTs, the other players of senile plaques primarily composed of extracellular amyloid-β (Aβ). Aβ is formed following sequential cleavage of the Amyloid Precursor Protein (APP) by two proteases like β- and γ-secretases. Subsequent formation, Aβ is self-aggregated into insoluble β-sheet structures that lead to the formation of extracellular plaques. The deposition of Aβ is an early event in the pathogenesis of AD that precedes the formation of NFTs and collectively is referred to as the beta-amyloid hypothesis [3,4]. Even though the presence of both plaques and tangles are central features associated with AD, but the link between these two characteristic pathologies has remained elusive. However, Aβ aggregates into oligomers and leading to the production of Reactive Oxygen Species (ROS), induction of oxidative stress and eventually cell death [5,6]. On the other hand, Aβ may lead to caspase activation through the initiation of apoptosis. The activation of caspases leads to the cleavage of critical cellular proteins including actin, fodrin and most importantly tau. The cleavage of these proteins may result in the breakdown of the cytoskeleton while the cleavage of tau may facilitate its hyperphosphorylation, leading to further instability in the cytoskeleton. Recent evidence suggests that caspases may be playing a vital role in the disease mechanisms underlying AD including promoting Aβ formation as well as linking plaques to NFTs [3-5].

Molecular Signalling of Aβ Mediated Synaptic Dysfunctions in AD

The molecular mechanism involved in oligomeric Aβ mediated synaptic dysfunctions in AD is very complicated. Oligomeric Aβ induced calcium dyshomeostasis that trigger caspases and calcineurin activations and modulated the activity of receptor tyrosine kinases, and finally initiated a cascade of molecular events that culminate in the inhibition of Long Term Potentiation (LTP), an electrophysiological correlate of memory formation and facilitation of Long Term Depression (LTD) of synapses. Impairments in LTP and facilitation in LTD ultimately causes synapse loss and impairment in synaptic networks [7]. LTP and LTD depend on the physiology of calcium influx through N-methyl-D-aspartate (NMDA) receptors along with the activation of metabotropic glutamate receptors (mGluRs) [8,9]. On the other hand, LTP is associated with dendritic spine enlargement and increase synaptic density whereas; LTD leads to dendritic spine shrinkage and synaptic collapse [7,10]. Numerous protein kinases such as p38 mitogen-activated protein kinase (MAPK), calcium calmodoulin-dependent protein kinase II (CaMKII), glycogen synthase kinase 3-beta (GSK3β), and ephrin receptor B2 (EphB2) have all been shown to altered LTP induction in the brain [7,11]. The phosphatases and proteases also such as calcineurin (protein phosphatase 2B [PP2B]) and caspases play a key intracellular roles in the initiation of LTD [7,12]. Oligomeric Aβ has been shown to inhibit LTP and enhance LTD by amending the activity of all of the above molecular signalling pathways. It has been shown that oligomeric Aβ induces partial blockade of NMDA receptor currents, which ultimately leads to the diminution of calcium influx into spines and that encouraged LTD over LTP [7]. The oligomeric Aβ- induced LTP impairment is considered to be involved in diminution in the MAPK, CaMKII and Akt/protein kinase B activation [13,14]. Aβ has also been revealed to induce synaptic depression through the activation of mGluRs, which ultimately promoting internalization of a-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptors and synapse collapse [7]. Caspase-3 activity has also been identified to be critical for oligomeric Aβ-mediated facilitation of LTD. Oligomeric Aβ activates caspase-3, which leads to LTD through the activation of different protein phosphatases that ultimately dephosphorylated AMPA receptors and supported their endocytosis from synaptic surfaces, suggesting
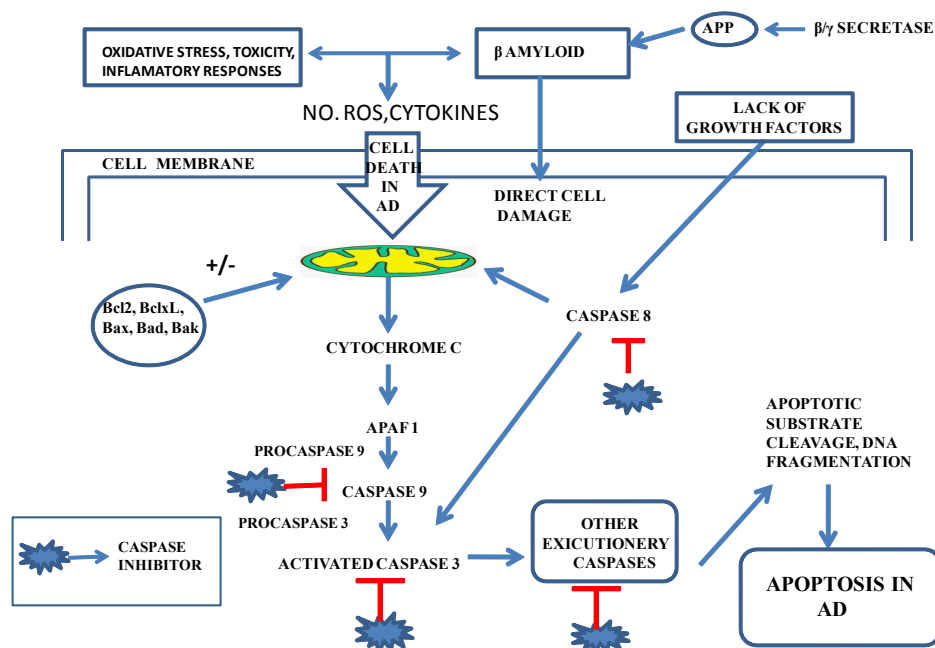
*Corresponding author: Dr. Kuladip Jana, Division of Molecular Medicine, Bose Institute, Centenary Campus, P 1/12, Calcutta Improvement Trust Scheme VIIM, Kolkata-700 054, India, Tel: 091-33-25693322/091-9007042850; E-mail: nagi.kuladip@bic.boseinst.ernet.in; kuladip_jana@yahoo.com

that prevention of caspase-3 activation may be a possible therapeutic approach for treatment of AD [13,14] (Figure 1).

Caspase Activation in AD

The progressive nature of neuronal cell dysfunction and death in AD is consistent with an apoptotic mechanism. This includes apoptotic morphology of degenerating neurons, TUNEL positive neuronal staining and alterations in gene expression profiles reflects an apoptotic state in neurons of AD subjects [15,16]. Indeed, recent studies also supports that caspase activation precedes and leads to the formation of NFTs [17-19]. Moreover, the study of Gastard et al. [20] demonstrated the activation of caspase-3 within immature tangles in subjects with mild AD and that supports for caspase activation as an early event in progression of AD [20]. Besides, Guillozet- Bongaarts et al. [21] also confirmed the truncation of tau by caspases may occur relatively in early state of the AD [21]. Caspase mediated cleavage of tau also interrelated with the formation of NFTs in AD. Studies from different groups, it is clear that caspase cleavage of tau as a proximal event and which is associated with the formation of NFTs and Aβ in AD [13,22-24]. In addition to the caspase-cleavage of tau, evidence suggested that APP is a substrate for caspase-mediated cleavage and this is an important early step in the disease process that may contribute to Aβ formation, synaptic loss, and the behavioral changes associated with AD [16,23,25]. Thus, the therapeutics that aimed on inhibiting the caspase-cleavage of tau may be a beneficial in not only preventing

NFT formation, but also slowing the cognitive impairment (Figures 1 and 2).

Role of Caspases in the Pathogenesis of AD

The caspases have been detected in brains of the patients suffering with AD. In fact, caspases-1, -2, -3, - 5, -6, -7, -8 and -9 have all been detected to be transcriptional elevated in AD [26]. Caspase-9 activity has also been found to be associated in the pathology of AD and caused for the NFT formation [26]. Caspase-9 was also involved directly to cleave APP, and ultimately caspase-9 may induce apoptosis in AD brains independent of caspase-3 or Apaf-1 [27]. Activated caspase-3 has also been detected in neurons of AD brains along with a co-localization of NFTs and senile plaques [26] suggesting the role of caspase-3 is an important role for synaptic degeneration during the AD progression [28]. In fact, caspase-3 primarily concerned in AD pathogenesis by cleaving tau in its C-terminal region and caspase-3-cleaved tau co-localizes with both intracellular Aβ and activated caspase-3 in AD brains. Ultimately, caspase-3 has also been shown to cleave APP, generating Aβ-containing peptides [26]. It is believed that Aβ plaque formation and toxicity is probably augmented in a caspase dependent manner. Caspase-6 is also capable of cleaving tau, and by that way it helps for aggregation in NFTs [19]. Altogether, it is very clear that caspases play an active role in the Aβ- induced neurotoxicity in AD. Therefore, therapeutics aimed at preventing the activation and execution of apoptosis through caspases inhibition may provide a

Figure 1: Molecular signalling involved in amyloid β (Aβ)-mediated synapse loss in Alzheimer's disease. In dendrites, accumulation of Aβ leads to mitochondrial stress, cytochrome *c* release, and caspase-3 activation. Caspase-3 activates calcineurin, which dephosphorylates AMPARs, leading to their subsequent removal from the post-synaptic density (PSD) and causing dendritic spine degeneration. Caspase-3 is also implicated in tau truncation and activation of GSK-3β. Tau truncation, together with GSK-3β- dependent tau phosphorylation, promotes neurofibrillary tangles (NFTs), contributing to synaptic degeneration.

Figure 2: Proposed causes of apoptosis and the role of caspases and its inhibitors in Alzheimer's Disease (AD): β Amyloid toxicity is the major cause of cell death in AD. β Amyloid peptides are generated from larger Amyloid Precursor Protein (APP) by the proteolytic actions of β and γ secretases. β amyloid causes cell death through inflammation, oxidative stress, as well as direct damage to the cell membrane. Death factors triggers mitochondria for the release of cytochrome c, this induces the activation of different apoptotic factors within the cell. Bcl2 family proteins includes a combination of pro-apoptotic (Bax, Bad, Bak) and anti-apoptotic (Bcl2,BclxL) proteins that regulate the permeability of mitochondrial membrane, regulating cytochrome c release. In the cytosol it combines with the Apoptotic Protease Activating Factor 1 (APAF1) and procaspase 9 to produce active caspase 9. Caspase 9 cleaves pro-caspase 3 to active caspase 3, that also induces other effector caspases. Caspases cleaves apoptotic substrates and causes DNA damage, resulting apoptosis. Lack of growth factor results in the activation of caspase 8, that can affect mitochondria as well as can form active caspase3.Caspase inhibitors stops the downstream caspase activation, as a result execution of apoptotic pathway get blocked and apoptosis cannot take place.

effective means of treating AD, and other neurodegenerative diseases in general.

Caspase Activation in AD: Studies on Animal Models

Even though there is a considerable evidence of the correlation of the caspases activation and a potential link between Aβ and NFT formation, but the studies on animal models were directly confirmed this hypothesis. LaFerla et al. developed a mouse strain, termed 3×Tg-AD mice and there is a progressive development of both plaques and tangles and the plaques taking place prior to tangle formation and that is in consistent with the amyloid cascade hypothesis [29]. Rohn et al. also generated a mouse strain which is over expressed of anti-apoptotic protein Bcl-2, termed as 3×Tg-AD/Bcl-2 [30]. Over expression of Bcl-2 in the neurons of 3×Tg-AD mice, blocked caspase activation and the cleavage of tau leading to its accumulation within neurons [30]. Even though in the presence of high tau protein, there was little evidence for neurofibrillary tangles formation in 3×TgAD/Bcl2 mice, and suggested that caspase-cleavage of tau is a crucial step leading to neurofibrillary tangles formation in AD. It has also been found that in 3×Tg-AD mice of over expressing Bcl-2, higher levels of intracellular APP was observed in cortical neurons compared to 3×Tg-AD mice alone. Recently, Cecconi et al. [14] reported that Aβ accumulation leads to aberrant caspase-3 activation triggering a cascade of down-stream signaling including an alteration in synaptic transmission along with tau phosphorylation, rather than the classical apoptotic pathway in the hippocampus of the Tg2576 mouse model that over-expresses human mutant amyloid precursor protein (Tg 2576-APP swe). Moreover, the APP transgenic Tg2576 mouse model develops memory dysfunction and loss of apical dendritic spines in the CA1 of the hippocampus in 3 months of age prior to the development of extensive amyloid plaques in that region. The change is also associated with the post-synaptic loss of the AMPAR GluR1 subunit. The authors reported that caspase-3 activation may occurs upstream of these changes, as the casapase-3 activity is increased in hippocampus in 3-month-old Tg2576-APPswe [14]. The results from these studies suggested a novel mechanism by which caspase activation contributes to the processing of APP and tau and suggests that caspases play a pivotal role in the initiation and progression of the pathology associated with AD.

Evidence that Caspases as Therapeutic Targets in the Treatment of AD

A critical involvement of caspases in the etiology associated with AD has been well recognized. Therefore, question may be raise as the targeted inhibition of this class of proteases can able to provide an effective means to treat this disease? To get the answer of this question, it might be worthwhile to discuss about the studies of pharmacological inhibitions of caspases to treat different neurodegenerative diseases. For example, Li et al. [31] used the pan-caspase inhibitor N-benzyloxycarbonyl-Val-Ala-Asp fluoromethyl-ketone (Z-VAD-fmk) to treat transgenic mice expressing mutant human SOD1, a model of amyotrophic lateral sclerosis (ALS). In this case, administration of Z-VAD-fmk delayed the disease onset and also mortality in ALS mice [31]. The post-synaptic loss of GluR1 in hippocampal slices of Tg2576-APPswe mouse model was reversed by the treatment of Z-DEVD-fmk and it also restored glutamatergic signaling and transgenic animal's behavioral dysfunctions [14]. The potential caspase inhibitor such as N-benzyloxycarbonyl-Val-Ala-Asp fluoromethyl-ketone (Z-VAD) have been investigated for the treatment of a number of

neurodegenerative disorders including amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease (PD), and finally acute neurologic diseases like ischemia or traumatic injury [31-33]. Unfortunately, clinical development of Z-VAD was discontinued as Z-VAD produces liver damage following the production of the toxic compound, fluoroacetate [34]. Following the disappointment of Z-VAD, a number of other caspase inhibitors have been developed with the aim in mind of being safer and more selective product. Quinolyl-valyl-O-methylaspartyl-(-2, 6-difluorophenoxy)-methyl ketone (Q-VD-OPh) is a newer, third-generation broad-spectrum caspase inhibitor that has very promising potential as a therapeutic compound [34]. The Q-VD-OPh is also showing far better compound than Z VAD in various aspects, like stability, selectivity, potency as well as cell permeability [34]. Q-VD-OPh also appears to be less toxic than Z-VAD even at very high dose. Most importantly, Q-VD-OPh appears to be able to cross the blood–brain barrier, which is always a central issue when developing a drug for treatment of any CNS disorders. Treatment with Q-VD-OPh in animal models of Parkinson's or Huntington's and/or stroke confirms its role as a neuroprotective agent [35,36]. Therefore, the Q-VD-OPh comes out to play as an interesting agent to prevent AD associated pathology. As we all know AD leads to neuro-degenerative changes, and now it would be better to test whether Q-VD-OPh can be able to prevent the pathology in AD animal models. Nowadays a second generation tetracycline, minocycline is under investigation in the treatment of neurodegenerative disorder. It is acting better than Q-VD-OPh, and it is in a Phase II PD clinical trial and Phase I/II clinical trial for spinal cord injury [37]. In addition, recently a Phase III clinical trial has been done with minocycline as a therapeutic agent for the treatment of ALS. Unfortunately, the results of the trial were negative [37]. The use of Minocycline in the treatment of AD may have immense hope in the future clinical trials. Preliminary studies have shown that administration of this compound improved behavioural deficiencies in Aβ infused rats [38]. However, in an another study using transgenic mice harboring the human APPsw and V717F mutations, it was found that the treatment with minocycline had a positive effect on reducing microglial activation but did not attenuate Aβ deposition or behavioral deficits in APP mice [38]. Minocycline administration leads to behavioural improvement and microglial suppression in younger mice. Minocycline is also able to slow down the levels of caspase 3 activation, of caspase induced cleavage of tau and Aβ induced neuronal death [39]. It has been reported that *in vivo* minocycline treatment in transgenic mice over expressing human tau, results in reduced phosphorylation of tau and its cleavage by caspase 3 [39]. This compound exhibits its activity against AD associated reactive microgliosis [3,40]. As a whole, minocycline is proving itself as an upcoming promising compound for the treatment of AD.

Toxicities of Caspase Inhibitors Used as Therapeutic Targets in the Treatment of AD

Before using any compound, acting as a potential caspase inhibitor in the treatment of AD, it is to be properly investigated whether it may impart any toxic effect in the body or system. There is no report of any such study with chronic treatment of caspase inhibitors in animal models. Existing literatures show certain data regarding toxicity profile, like Chauvier et al. [41] suggested the absence of any toxic effects of Q-VD-OPh after its acute treatment in mice [41]. Structurally similar compound IDN- 6556, a caspase inhibitor, is also proven to be safe in human at a dose up to 10 mg/kg/infusion for a single dose in Phase I clinical trial [42]. Minocycline has shown little toxicity in ALS and PD, Phase I clinical trials [37]. In recent Phase III trial of minocycline, the patients were declined faster than those on placebo [43]. There are

lot of difference between Q-VD-OPh and minocycline regarding the toxicological impact as because they are only linked by the selective effect of caspase inhibition and therefore, the toxicological studies of such compounds should be done properly in AD animal model to know the putative efficiency of such compounds.

Drug Delivery System in the Treatment of AD with Caspase Inhibitors

Alzheimer's disease prevalence is increasing, but the efficacy of treatment is still very limited due to the protective barriers of the Blood Brain Barrier (BBB). Drug delivery to the brain remains the major challenge for the treatment of Alzheimer's disease because of the barriers surrounding the central nervous system. The new therapeutic drugs that cross the BBB are critically required for treatment of several brain diseases including alzheimer's disease [44]. Nanoparticles drug delivery systems including liposomes, polymers, and other nanoparticles may be able to provide the potential solutions to improve neurodegeneration therapeutics. Moreover, among these drug delivery systems, liposome-based agents will have the greatest impact in neurological disorders. With the applications of liposomal technology, the development of a suitable liposomal carrier to encapsulate neuro-protective compounds like caspase inhibitors is very promising. The liposomes are stable enough to be carried to the brain across the BBB, for an effective targeting of the affected area [44]. The rapid development of liposome technology may provide a novel solution in neurotherapeutic challenges for neurodegenerative diseases such as Alzheimer's disease.

Conclusions

Presently, there are only a few FDA-approved medications available for AD patients and these medications are palliative in nature. Over a decade of research has supported a role for the activation of caspases in the AD brain, and recent studies has indicated an involvement of this pathway in promoting the pathology underlying this disease. There are lot of evidences that supports the association of caspases in the neurodegenerative changes in AD. It is of great interest to study the detailed apoptotic mechanism playing behind the pathological changes in AD. Until different animal model studies in AD is not done, the treatment with various compounds like Q-VD-OPh or minocycline brings no worth of importance. Moreover, the liposomes may need to be tested clinically as the improved nanoparticles based drug delivery of chemotherapeutic agents like caspase inhibitors for the management of AD. Therefore, more serious and detailed pre-clinical studies are needed for the future drug development of these compounds in the treatment of AD.

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