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A Conclusive Review on Amyloid Beta Peptide Induced Cerebrovascular Degeneration and the Mechanism in Mitochondria

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Abstract

Promising evidence suggests that amyloid beta peptide (Aβ), a key mediator in age-dependent neuronal and cerebrovascular degeneration, activates death signalling processes leading to neuronal as well as non-neuronal cell death in the central nervous system. A major cellular event in Aβ-induced apoptosis of non- neuronal cells, including cerebral endothelial cells, astrocytes and oligodendrocytes, is mitochondrial dysfunction. The apoptosis signalling cascade upstream of mitochondria entails Aβ activation of neutral sphingomyelinase, resulting in the release of ceramide from membrane sphingomyelin. Ceramide then activates protein phosphatase 2A (PP2A), a member in the ceramide-activated protein phosphatase (CAPP) family. PP2A dephosphorylation of Akt and FKHRL1 plays a pivotal role in Aβ-induced Bad translocation to mitochondria and transactivation of Bim. Bad and Bim are pro-apoptotic proteins that cause mitochondrial dysfunction characterized by excessive ROS formation, mitochondrial DNA (mtDNA) damage, and release of mitochondrial apoptotic proteins including cytochrome c, apoptosis inducing factor (AIF), endonuclease G and Smac. The cellular events activated by Aβ to induce death of non-neuronal cells are complex. Understanding these apoptosis signalling processes will aid in the development of more effective strategies to slow down age-dependent cerebrovascular degeneration caused by progressive cerebrovascular Aβ deposition.

Key words: Aging, Amyloid beta Peptide, Apoptosis, Ceramide, Cerebrovascular Disease, Endothelial Cells, Mitochondria Alzheimer's Disease

1. Introduction

Cerebrovascular obstruction is the second leading cause of death and the leading cause of adult disability worldwide according to World Health Organization statistics. Age is the most important stroke risk factor[1,2]. The burden of stroke on the health care system and the society as a whole is likely to aggravate with accelerated aging of the population. Vascular dementia is also a serious burden to families and the society. This review on Aβ in Cerebrovascular degeneration focuses on mitochondrial dysfunction affecting cerebral endothelial cells (CECs) with selected ancillary ndings on other cell types. Extensive works by a number of distinguished investigators on Aβ effects in vascular smooth muscles, particularly Dr. W.E. Van Nostrand's group, are not extensively covered because of space constraints.

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1.1. Aging and Cerebrovascular Diseases

Promising evidence suggests that cerebrovascular function declines with aging[1,3-8]. Atherosclerosis is an important cause of age-dependent degeneration of large arteries. However, another aging process that affects primarily the microvessels has emerged in the study of the aging brains, particularly those with Alzheimer's disease (AD). The cerebral vasculature appears to share a common fate with the brain parenchyma in age-dependent amyloid deposition. With aging, cerebrovascular changes include decreasing number of endothelial cells, thinning of the capillary wall, and reduced endothelial mitochondrial density[9,10].

1.2. Amyloid in the Cerebral Vasculature

Amyloid deposition in the brain is an aging process noted widely in primates and other species[11,12]. Research on the pathology and molecular mechanisms of AD has focused primarily on amyloid deposition in the brain parenchyma. The cerebral vasculature is also a primary target of amyloid deposition resulting in cer-

ebral amyloid angiopathy (CAA) in the aging brains with or without AD[7,13-19]. Studies in hereditary types of CAA (Dutch and Icelandic, and others) show that amyloid deposition may occur predominantly in the cerebral vasculature[20-26]. Recent data from brain imaging studies in humans and animal models suggest that cerebrovascular dysfunction may precede cognitive decline and onset of neurodegenerative changes in AD and AD models[27]. Cerebral hypoperfusion and impaired amyloid β-peptide (Aβ) clearance across the blood brain barrier (BBB) may contribute to the onset and progression of AD[18,28-30]. CAA is a major stroke risk factor the elderly causing hemorrhagic or ischemic strokes[1,19,25,31-33]. Patients with CAA may present clinically with recurrent strokes with or without dementia[34-38]. Vascular amyloid deposition is accompanied by dysfunction and loss of mitochondria in endothelial cells. Endothelial cell death may contribute to vascular degeneration[3,9,10,15,39]. Other features of amyloid angiopathy are thickening of the basement membrane, irregularities of vasculature, alteration of collagen content[3,7,14,40], and vascular smooth muscle degeneration[40-43]. Understanding the molecular mechanism of amyloid-induced cerebrovascular degeneration may contribute to the development of stroke preventive measures in the elderly.

1.3. Amyloid β Peptide (Aβ)

The major component of amyloid deposits in the brain parenchyma and cerebral vasculature is a small and unique peptide, amyloid β (Aβ)[33,44]. The cellular origin of Aβ that causes CAA remains to be fully dened[45,46]. Aβ is a 39-43 amino acid peptide derived from proteolytic cleavage of the amyloid precursor protein (APP)[47]. Aβ has been consistently demonstrated in senile plaques and leptomeningeal and intracortical vessels in the AD brains but to a lesser extent in the aging brain without AD. Aβ peptides that accumulate in the AD brains are heterogeneous. Aβ1-40 and Aβ1-42 are the most commonly encountered species. In some AD brains Aβ1-42 may be the dominant peptide in the senile plaques, while the dominant species in cerebral vasculature is Aβ1-40[7,48-53]. The demonstration of APP mRNA in the vascular wall supports the contention that locally derived Aβ contributes to cerebrovascular degeneration in aging brains including those with AD and hereditary CAA[54]. Recent studies suggest that Aβ accumulation in the AD brain is likely due to its impaired clearance from the brain[55,56]. LDL receptor-related protein 1 (LRP1) is a major Aβ transporter at the BBB[30,57]. Binding of Aβ to LRP1 initiates Aâ clearance from brain to blood via transcytosis across the BBB[18,28]. Aβ may also be eliminated by proteolytic degradation[58]. In addition, soluble Aβ probably originates from the peripheral circulation as well as the cells within the central nervous system[59,60]. Human platelets contain high levels of APP, which may contribute to more than 90% of the circulating APP[61]. Platelet APP may also be the major source of Aβ detected in whole blood[62]. Aβ is released upon platelet activation[63]. The main species of Aβ released from activated human platelets is Aβ1-40, consistent with the contention that circulating Aβ contributes to vascular amyloid deposits dominated by Aβ1-40[64]. However, exceptions have been noted[23]. The relative importance of different Aβ fragments in CAA remains to be fully dened.

1.4. Aβ and Cerebrovasculature Degeneration

Aâ has been implicated as the primary neurotoxic factor in the pathogenesis of AD[65]. Many lines of studies have shown that Aβ is also cytotoxic to non-neuronal cells including CECs[66-76], cerebrovascular smooth muscle cells[77], oligodendrocytes[78,79], and astrocytes[80]. In addition to neuronal degeneration, cerebrovascular alterations indicative of damage to vascular endothelial cells and disruption of the BBB occur in AD[5,81]. Aβ also impairs BBB function in vitro[82] and in vivo[72]. Since CECs and astroglia are the two major constituents of BBB to shield the brain from damage by harmful circulating toxins or deleterious cellular elements, Aβ induced death of these two cell types may lead to the disruption of BBB[16,18,30,56]. Other detrimental or angiopathic effects of Aβ include arterial hypercontractility, cerebral blood ow dysregulation[17], enhancement of endothelial permeability and defective glucose transport[72,82]. Aβ deposition may also increase brain vulnerability to ischemic injury[83,84], probably related to its additional vascular effects, including platelet aggregation[85], leukocyte activation, promotion of inammatory reaction[86,87], inhibition of endothelial proliferation[16,88], alteration of Cerebrovascular reactivity[89], disruption of the basement membrane[90] and increase in BBB permeability[91]. Overall, Aβ appears to cause multiple detrimental effects in the pathogenesis of age-dependent angiopathy. Findings characterizing the

cell death pathways that underlie Aβ cytotoxicity in non-neuronal cells including CECs and astrocytes may aid in preserving BBB integrity and slow down age-dependent cerebrovascular degeneration.

2. Mitochondrial Mechanisms in Aβ-induced Non-neuronal Cell Death

2.1. Aβ Induction of Mitochondrial Dysfunction

Mitochondrial dysfunction may be a major mechanism of aging and neurodegenerative disorders including stroke. Accumulating evidence suggests mitochondrial dysfunction may trigger apoptosis[92-95] and is a key mechanism of cell death in disease states[96]. This has led to a renaissance on the study of this organelle. Because mitochondria are the major consumers of molecular oxygen within cells, they stand as one of the most important generators of reactive oxygen species (ROS). Mitochondria are a primary target of therapeutic interventions in pathologic states involving oxidative stress and apoptosis[96-100].

Aβ induced CEC death is characterized by a number of biochemical and morphologic features indicative of apoptosis[73,76]. Aβ1-40 was noted to be more potent than Aβ1-42 in causing endothelial cell death[101,102]. Aβ25-35, a synthetic fragment of Aβ, which shares selected Aβ effects, is also cytotoxic to CECs[71,73,76]. Aβ cytotoxicity was thought to be related to excessive formation of ROS such as superoxide and can be suppressed by antioxidants[73,103]. Aβ activation of caspases is accompanied by mitochondrial DNA (mtDNA) damage, and mitochondrial dysfunction[73,104]. Events associated with Aβ-induced mitochondrial dysfunction leading to apoptosis include excessive ROS formation, and release of mitochondrial apoptotic proteins such as cytochrome c, apoptosis inducing factor (AIF), endonuclease G (endoG)[105] and Smac[73,74,105]. A consequence of excessive mitochondrial ROS formation is mtDNA damage. Cumulative mtDNA damage is a cellular marker of aging[106]. mtDNA damage caused by Aβ can further compromise mitochondrial function, feeding another positive loop of apoptosis.

2.2. The Neutral Sphingomyelinase-ceramide Cascade

The molecular mechanism of Aβ induced mitochondrial dysfunc-tion and subsequent cell death in non-neuronal cells remains to be fully dened. It appears oxidative stress induced by Aβ contributes to its cytotoxicity[73,101]. Ceramide is a lipid mediator that also causes excessive ROS formation and subsequent apoptosis in a number of cell types[107]. Since both Aβ[73,104] and ceramide[108] share common features in death signalling processes (mitochondrial dysfunction and excessive ROS generation), efforts have been devoted to explore whether ceramide is a mediator of Aβ-induced apoptosis in non-neuronal cells including CECs, astrocytes, or oligodendrocytes[79,80,109]. To dene the causal role of a ceramide synthetic pathway in Aβ-induced cell death, there are at least 3 putative enzymes for cellular ceramide formation to explore. Two of these involve the degradation of sphingomyelin by sphingomyelinase (SMases) to release ceramide. Neutral SMase (nSMase) and acidic (aSMase) are respectively implicated in a number of cell death paradigms[108,110,111]. The 3rd cascade entails de novo ceramide synthesis catalyzed by ceramide synthase[109]. Increase in nSMase activity is linked to cellular senescence[112]. nSMase has also been identied in cerebral microvessels[113]. We demonstrated that Aβ-induced non-neuronal cell death is accompanied by an increase in ceramide content. This increase is causally related to Aβ activation of nSMase, but no aSMase or ceramide synthase[79]. Furthermore, selective nSMase inhibitors[79] or nSMase gene knockdown[80] blocked Aβ-induced cell death. Together these ndings support a causal role of the nSMase-ceramide cascade in Aβ-induced mitochondrial dysfunction and non-neuronal cell death and open a preventive or therapeutic avenue directed at the nSMase-ceramide cascade for blocking Aβ-induced non-neuronal cell death (Fig. 1).

2.3. Protein Phosphatase 2A downstream of the nSMase-ceramide Cascade

Reversible protein phosphorylation catalyzed by protein kinases and protein phosphatases regulates various cellular processes, including apoptosis[114]. Recent studies have highlighted a major role of serine/threonine protein phosphatases, including protein phosphatase 2A (PP2A) in apoptosis[115]. PP2A, a member of the ceramide-activated protein phosphatases (CAPPs) family, regulates the activities of several major protein kinase families, including Akt. Akt dephosphorylation leading to Bad activation is a critical step in the initiation of

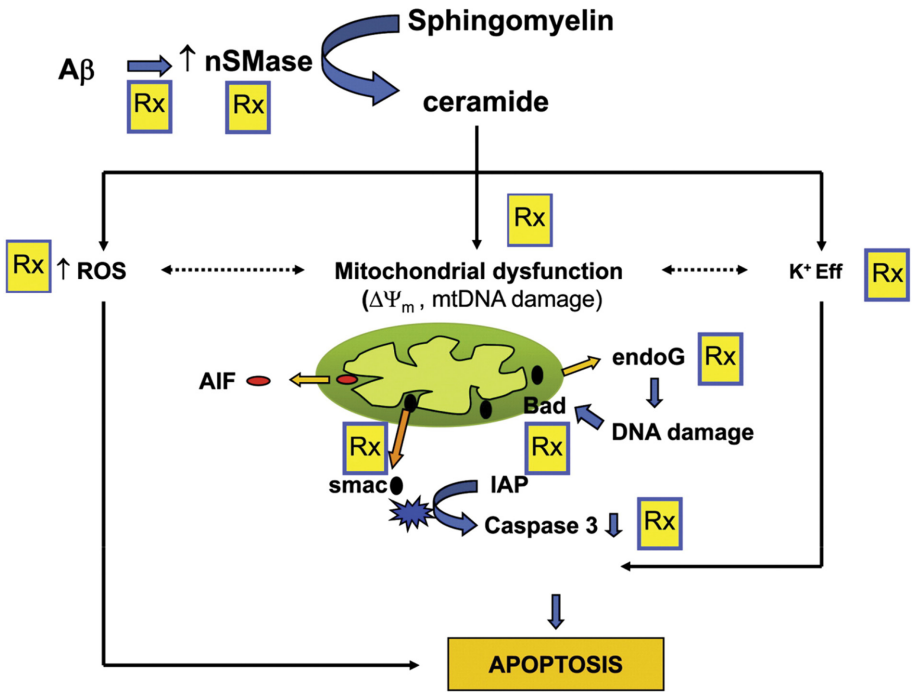

Fig. 1. Schematic summary of Aβ induced mitochondrial dysfunction. Aβ-induced mitochondrial dysfunctions leading to apoptosis include excessive ROS formation, and release of mitochondrial apoptotic proteins such as apoptosis inducing factor (AIF), endonuclease G (endo G) and Smac. Excessive ROS formation cause by Aβ can damage mitochnondrial DNA (mtDNA) and compromise mitochondrial function, feeding another positive loop of apoptosis. "Rx" represents as potential targets to prevent Aβ cytotoxicity in non-neuronal death and to slow down cerebrovasculature degeneration caused by amyloid deposition. K+ Eff: potassium ion efux.

apoptosis[116]. In addition, the ceramide-PP2A cascade has been shown to regulate the mitochondrial permeability transition pore (PTP) causing cytochrome c release. This pathway plays a crucial role in mitochondrial dysfunction and cell death and is mediated by Bad[117]. Akt, an upstream regulator of Bad, is important in mediating survival of vascular endothelial cells[104,118-120]. Upon phosphorylation at Ser473, Akt promotes cell survival via phosphorylation and inactivation of downstream targets such as the glycogen synthase kinase-3β (GSK-3β)[121] and pro-apoptotic Bcl-2 family members Bad[122]. Recent studies further demonstrated that Akt play a crucial role in stroke and identied that the Akt cascade as a therapeutic target for the amelioration of brain injury and cognitive decits[123,124]. The role of PP2A in Aβ-induced non-neuronal death is further strengthened by the causal relation of its activity to cell viability[75,76]. Thus ceramide activation of PP2A may play a causal role in Aβ death paradigms by dephosphorylation of Akt. In addition to promoting cell survival via transcription-independent mechanisms, Akt phosphorylates and inactivates the FOXO subfamily of Forkhead box transcription factors like FKHRL1, which promote transcription of pro-death genes[122]. In agreement with these observations, the Akt-Bad[105] and Akt-FKHRL1-Bim[75] cascades are altered by Aβ, resulting in CEC death. These ndings together suggest that activation of the nSMase-ceramide-PP2A-Akt cascade leading to mitochondrial dysfunction may be pivotal in the development of CAA and subsequent cerebrovascular degeneration and stroke (Fig. 2).

2.4. Aβ-activated Death Signalling Cascade Downstream of Mitochondria

Aβ-induced CEC death is associated with mitochondrial release of cytochrome c, endo G and Smac. Smac binding to X chromosome linked inhibitor-of-apoptosis protein (XIAP) and caspase activation are Aβ-activated death signaling processes downstream of mitochondria[73,74,105]. These intermembranous proteins that are

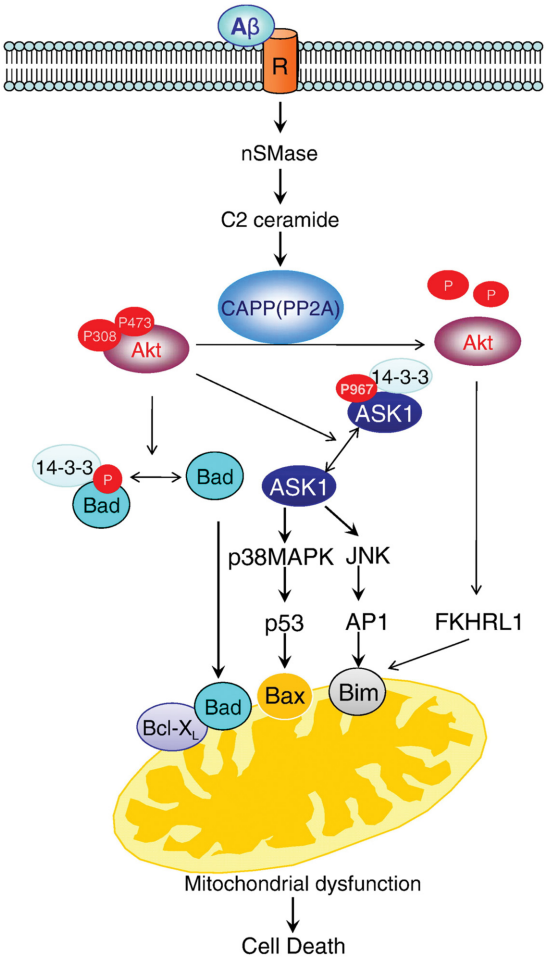

Fig. 2. Schematic summary of the signaling cascade upstream of mitochondria in Aβ-induced cell death. Aβ activates neutral sphingomyelinase (nSMase) to catalyze sphingomyelin resulting in ceramide release. Ceramide then causes protein phosphatase 2A (PP2A) activation leading to Akt dephosphorylation at Thr308 and Ser473 and subsequent Bad translocation and Transactivation of Bim. Aβ activation of PP2A also results in ASK1 Ser967 dephosphorylation and subsequent release from ASK1-14-3-3 complex. ASK1 then activates JNK-AP1-Bim or p38MAPK-p53-Bax cascades to induce mitochondria dysfunction and cell death. "R" represents as a putative Aβ receptor.

released after Aβ exposure are controlled by the interaction of Bcl-2 family members on the mitochondrial membrane. The Bcl-2 family proteins regulate mitochondria-dependent death mechanisms, with the balance of the antiapoptotic and pro-apoptotic members arbitrating the life-or-death decisions[125]. Bim, a BH3-only protein, normally associates with cellular microtubule complexes but translocates to mitochondria shortly after apoptotic stimuli[126]. Bim expression induced by Aâ is through the AP-1[74] and FKHRL1[75] mechanisms and is causally related to mitochondrial release of Smac to bind XIAP, resulting in caspase activation and CEC death[74].

The involvement of another pro-apoptotic member, Bax, has also been implicated. Bax knockdown prevents Aâ-induced CEC death[76]. Bad, another BH3-only protein, downstream of Akt, is also linked to Aβ-induced non-neuronal apoptotic death[105] as described earlier. It is likely that activation of diverse pathways culminates in Bim and Bax expression and Bad activation, respectively. These pro-apoptotic Bcl-2 family proteins may act in concert to mediate Aâ-induced CEC death. However, whether Bim, Bad and Bax act in sequence or in synergy remains controversial[127]. Additional works are needed to characterize the interrelationship among these Bcl-2 family proteins in Aβ-induced mitochondrial dysfunction and subsequent non-neuronal cell death.

In the context of Aβ apoptotic actions on non-neuronal cell, several cell death regulatory signalling pathways upstream of these pro-apoptotic Bcl-2 family proteins have been identied. Activation of the c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) has been noted and appears to be critical in mediating Aβ-induced cell death[105,128]. Upstream of the MAPK cascade is apoptosis signal-regulating kinase 1 (ASK1) that is known to activate JNK or p38MAPK via MKK4/7 or MKK3/6 in response to oxidative stress, endoplasmic reticular stress, DNA damage, or inammation[129]. We have recently identied ASK1 as a novel target for Aβ to induce cell death through the PP2A pathway[76] (Fig. 2).

2.5. Other Cellular Events Relevant to Aβ-induced Cerebrovascular Degeneration

Platelet is another non-neuronal target of Aβ. Aβ-induced platelet aggregation involves activation of a p38MAPK signaling pathway[85]. Further studies are needed to dene the specic role of Aβ activation of platelets in the pathogenesis of vasculopathy including cerebral amyloid angiopathy and stroke. The signaling events of Aβ action upstream of nSMase activation

have not been delineated but are likely to involve Aβ interaction with cell membrane proteins. Multiple proteins have thus far been proposed as the candidate Aβ receptor. They are the receptor for advanced glycation end products[130,131], the endoplasmic-reticulum Aβ-binding dehydrogenase[130], α 7 nicotinic acetylcholine receptor[132], the formyl peptide receptor like-1[133], and the 75-kDa neurotrophin receptor[134]. These ndings raise the possibility of a receptor mechanism in Aβ-induced non-neuronal death.

3. Development of Pharmacological Interventions in CAA

Currently, there are no effective regimens for preventing cerebro-vascular degeneration caused by age-dependent cerebrovascular amyloid deposition. Vascular amyloid deposition alters the integrity of BBB[16,55,90] which is constituted by CECs and astrocytes. Therapies directed at these 2 cell types via a vascular route may be more efcacious than those envisioned through the CNS approaches for AD. There is also a distinct possibility that slowing down the pace of cerebrovascular degeneration may also delay neurological deterioration caused by AD[135]. Recent studies suggest that transport of Aβ among blood, the brain, and cerebrospinal uid may be regulated[16,18,30,56], offering new insights into pharmacological modulation of vascular amyloid deposition. The Aβ→nSMase→ceramide→PP2A→MAPKs cascade represents a death signalling pathway that may be amenable to therapeutic interventions to block Aβ-induced mitochondrial dysfunction in non-neuronal cells in the brain to slow down deterioration of cerebrovascular function and degeneration of the cerebrovascular structure. Blockade of the Aβ-activated death signalling processes can be achieved by pharmacological modulation of nSMase and PP2A activity, ROS formation or genetic manipulations of PP2A, Akt, ASK1 and p38MAPK to maintain mitochondrial integrity as demonstrated in recent studies[75,76,79].

4. Concluding Remarks

Aβ-induced mitochondrial dysfunction in non-neuronal cells in the brain may play a key role in CAA. Further studies directed at the molecular mechanism that underlies Aβ alteration of mitochondrial function are needed to develop therapeutic or preventive measures to reduce age-dependent increase in stroke risks.

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