Role of Reactive Oxygen Species (ROS) and Cytokines in Vascular Dementia: A Review

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Review Article

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Abstract

Vascular dementia (VaD) causes impairment of memory and cognitive functioning due to reduction in the blood flow and oxygen supply to the brain. Vascular dementia is the second most common type of dementia after Alzheimer's disease. When the blood supply to the brain is interrupted, brain cells are deprived of vital oxygen and nutrients, causing damage to the cortex of the brain - the area associated with learning, memory, and language. Vascular disease affects multiple cell types within the neurovascular unit (NVU), including brain vascular cells (endothelial cells, pericytes, and vascular smooth muscle cells), glial cells (astrocytes and microglia), with rise in inflammatory mediators (TNF-α, NF-kB, ROS, MAPK, TGF-β, IL-1, IL-6 and cytokines. Globally in different population the causes of dementia may be mixed. Vascular dementia arises as a consequence of ischemic insults such as hemorrhage and hypoperfusion that trigger neurodegeneration. The deprivation of nerve cells from oxygen and glucose results in depletion of nerve cell structural integrities responsible for VaD. There are number of evidences which causes neuronal loss like excitotoxicity through over calcium influx by NMDA receptor, increase ROS level produces symptoms of VaD.

Keywords: Vascular dementia (VaD), vascular cognitive impairment, Cytokines

Introduction

Vascular dementia is CNS disorders, which consequently cause cognitive impairment (dementia) attributable to cerebrovascular pathology. The term 'dementia' is described to various symptoms that occur due to excessive neuronal damage by specific diseases. These diseases include Alzheimer's disease and vascular dementia. Someone with dementia may experience loss of memory, mood changes, and problems with language [1, 2]. To be healthy and function properly, brain cells need a good supply of blood. Blood is delivered through a network of blood vessels called the vascular system. If the vascular system within the brain becomes damaged and blood cannot reach the brain cells, the cells will eventually die [4]. This can lead to the onset of vascular dementia. Given the importance of small vessel disease in vascular dementia and vascular cognitive impairment, it is reasonable to suggest that cognitive dysfunction results at least in part from interruption of axonal connections between one part of the cerebral cortex and another, and between the cerebral cortex and deep grey matter [6, 7]. Small vessel disease affects particularly frontal lobe white matter and the closely related basal ganglia, so it is not surprising that the cognitive dysfunction commonly seen in vascular dementia involves executive activity which is known to be a function of the frontal lobe [9]. Cerebral amyloid angiopathy may also affect white matter function because this is the final destination for the blood flowing in the cortical arterioles affected by this condition. In macro infarction, lacunas and micro infarction, it is the loss of neurons that is thought to be important and there is evidence that after a stroke, dementia is

more likely if the stroke was severe, therefore destroying more neurons [5]. This cerebral ischemia are energy failure occurs due to subsequent events including inflammation, glutamate-mediated excitotoxicity, calcium overload, initiation of intracellular death pathways, oxidative stress produces structural and functional changes occur. Mediators of these events interact with each other and contribute to cellular damage, in which a cholinergic deficit is involved, and finally cause cognitive impairment or dementia [13]. There are different types of vascular dementia stroke related dementia, sub cortical vascular dementia, mixed dementia. Many of the factors that increase the risk of vascular dementia are the same as those that increase the risk of cardiovascular disease (like smoking). a medical history of stroke, high blood pressure, high cholesterol, diabetes (particularly type II), heart problems or sleep apnea, a lack of physical activity [4, 5]. Always consult a doctor if you experience any sudden symptoms, such as slurred speech, weakness on one side of the body or blurred vision even if they are only temporary. These symptoms may be caused by temporary interruptions in the blood supply within the brain. Treatments are available but the vascular dementia progresses vary from person to person. Although the brain damage that causes vascular dementia cannot be reversed, it may be possible to slow the progression of the disease in a number of ways [10, 11]. These are number of medications used treat any underlying conditions, such as stroke, high blood pressure, high cholesterol, diabetes or heart problems adopting a healthier lifestyle by stopping smoking, taking regular exercise, eating healthily to regain their lost functions [14]. The FDA has issued guidelines on drug treatments for Alzheimer's disease (including cholinesterase inhibitors and memantine), but has not recommended these same drugs for treating vascular dementia. These drugs may, however, be prescribed to treat mixed dementia, particularly when Alzheimer's disease is predominant [16].

2. Pathophysiological role of inflammatory mediator in vascular dementia

1. Role of Stress in vascular dementia

Vascular dementia are the most common types of dementia with the former being the most predominant. Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates [45]. Key anti-oxidants include $O_2^{\cdot-}$ dismutases (SOD), glutathione peroxidases, and catalase. ROS can be generated by multiple enzymes within the vasculature as well as non-enzymatic sources. $O_2^{\cdot-}$ anion is the parent ROS molecule produced by the one electron reduction of molecular oxygen by various oxidases (e.g., NADPH oxidase, cyclooxygenase, enzymes in the mitochondrial electron transport chain, lipoxygenases, cytochrome P450 enzymes). $O_2^{\cdot-}$ can then be dismutase by SOD, resulting in the generation of hydrogen peroxide. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA [41, 43]. The increase the level of reactive oxygen species is responsible for suppresses apoptosis and promotes proliferation, invasiveness and metastasis. An increased level of reactive oxygen species in the vasculature, reduced nitric oxide bioavailability, and endothelial dysfunction leading to vascular disease is associated with vascular dementia. Elevated reactive oxygen species production causes neuronal cell death and damage [41, 43]. Oxidative stress reduced the nitric oxide and increase Amyloid-beta& ApoE4.These oxidative stress include in increase the reactive oxygen species because effecting by aging and homocystein. Proteasome inhibition cause neuronal dysfunction and neuronal death can produce a vascular dementia [41, 42]. When the blood supply to the brain is reduced by a blocked or diseased vascular system, vascular dementia occurs and leads to a progressive decline in memory and cognitive function [29]. Chronic cerebral hypoperfusion can be induced by

permanent bilateral common carotid artery occlusion in rats, resulting in significant white matter lesions, learning and memory impairment and hippocampal neuronal damage are cause vascular dementia [30].
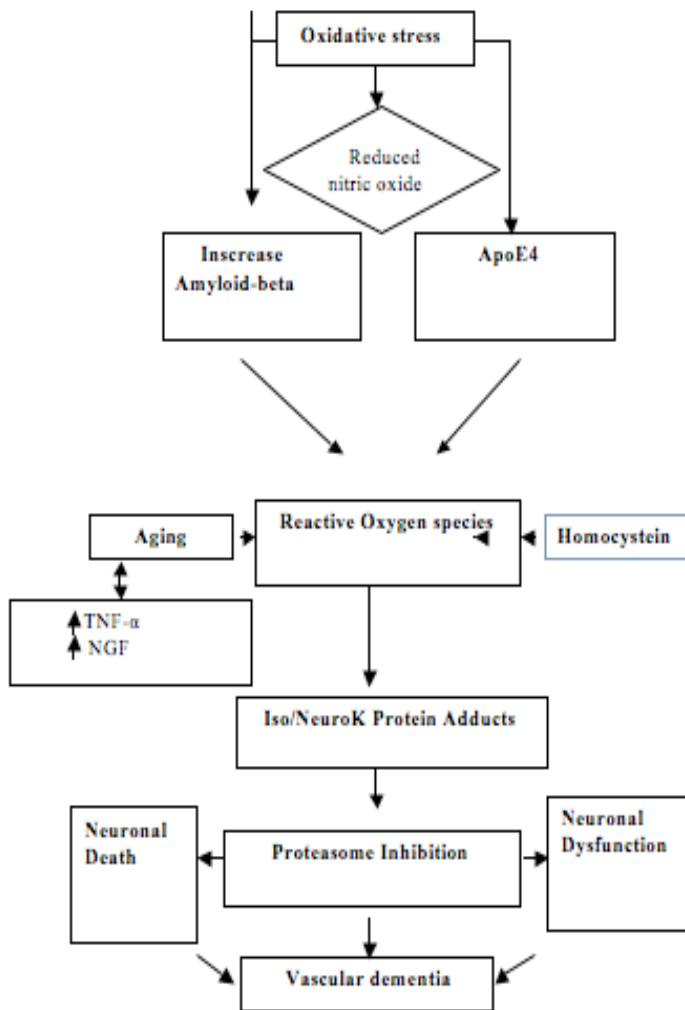

Fig1. Role of oxidative stress in vascular dementia

2. Effects of angiotensin II on the cerebral circulation: role of oxidative stress

Angiotensin II (Ang II) promotes oxidative stress in the vasculature via stimulation of AT1 receptors and subsequent activation of NADPH oxidases. Oxidative stress contributes to blood-brain barrier (BBB) dysfunction, impairment of vasodilation and neurovascular coupling, and promotes to vascular remodeling and inflammation [59].
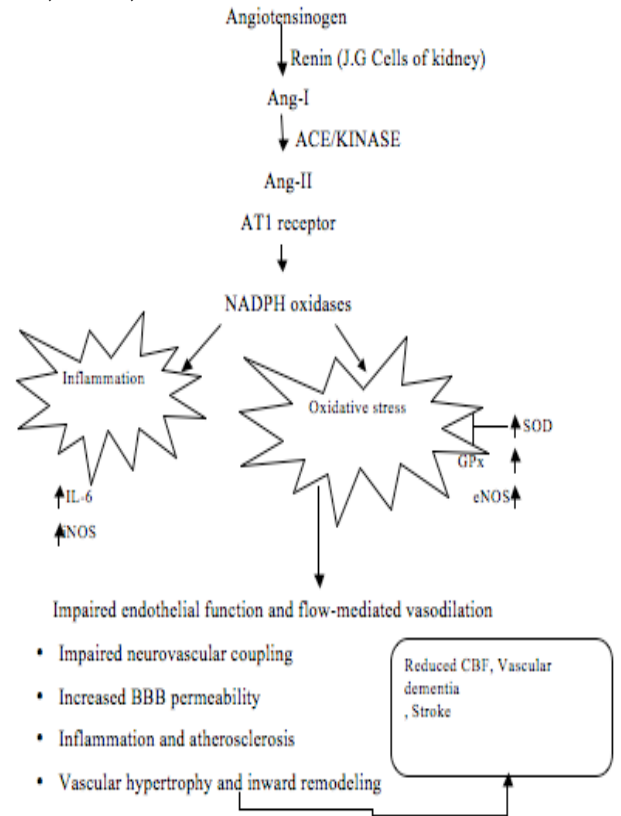
3. Role of cytokins and other inflammatory factors

Vascular dementia characterized by severe neurodegenerative changes, such as cerebral atrophy, loss of neurons and synapses [41]. The Central Nervous System (CNS) has its own resident immune system, in which glial cells serve as a supportive and nutritive role for neurons [69]. The evidence inferred a close association of neuroinflammation with the pathogenesis of several degenerative neurologic disorders, including AD [30]. Reactive astrocytes can contain substantial amounts of different forms of amyloid beta, including amyloid beta 1-42 (Aβ42) as well as truncated forms (38, 39). Reactive astrocytes can take up and degrade extracellular deposits of Aβ42 fig.3 and that this function is attenuated in ApoE-/-astrocytes suggesting that reactive astrocytes functions or dysfunctions could play a role in the progression and severity of AD. The intensity of reactive astrogliosis, as determined by Glial Fibrillary Acidic

Protein (GFAP) levels, has been reported to increase in parallel with increasing progression of pathological stages in AD [40]. These normal glial functions can sometimes result in a more severe and chronic neuroinflammatory cycle that actually promote or propagate neurodegenerative disease [28]. The pathological hallmarks of AD are senile plaques, neurofibrillary tangles and neuronal degeneration. Activated astrocyte and microglia produces a variety of proinflammatory mediators and neurotoxic factors, including cytokines, such as tumor necrosis factor (TNF-α); interleukin-1β (IL-1β); anti-inflammatory cytokine (IL6, IL10, IL4) and free radicals, such as Nitric Oxide (NO) and superoxide [67].
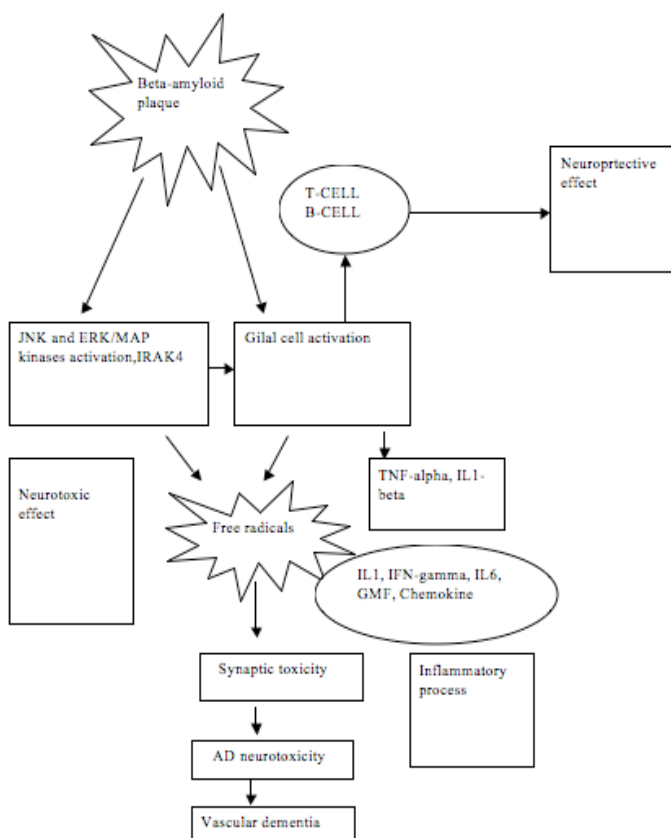

Fig.2 β amyloid plaque accumulation induced vascular dementia

Astrocytes respond to ongoing synaptic activity by mobilizing intracellular Ca^{2+}, leading to the release of pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6. The inflammatory reactive glial cells can be neuroprotective by releasing anti-inflammatory cytokines, such as IL-10 and IL-4 [56]. Achieving a balance between overproduction of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines may be one way to regulate an inflammatory response [66]. Activated astrocytes can also inhibit microglial activities and can exert inhibitory effect on microglia. Astrocytes also have been reported to decrease the production of NO, Reactive Oxygen Species (ROS) and TNF-α from microglia. Thus the increased free radical generation, Nitric Oxide Synthase (NOS) gene expression may be activating microglia and astrocyte that may lead to the formation of proinflammatory cytokines ultimately leading to synaptic dysfunction which is an important pathophysiological component of VaD [53].

Glial activation, apoptosis and synapse function showing that glial activation, TNF-α and NF-κB nuclear factor-kappa B activation modifies long-term depression and potentiation of synaptic transmission in the hippocampus provides further evidence that anti-apoptotic signaling can modulate synaptic plasticity [23]. Finally, changes in mitochondrial membrane permeability in synaptic terminals have been associated with impaired synaptic plasticity in the hippocampus suggesting a role for apoptotic actions in synaptic function.

Apoptosis plays a significant role in cell death during neurodegenerative disorders such as AD [26]. A cascade of events like activation of caspases and aspartate-specific cysteine proteases has been proposed to play a key role in apoptosis. Over activation of glutamate receptors can induce apoptosis by a mechanism involving calcium influx [33]. Biochemical mechanism involved in apoptosis can be activated in synaptic terminals, where it can alter synaptic function and promote localized degeneration of synapses [38].
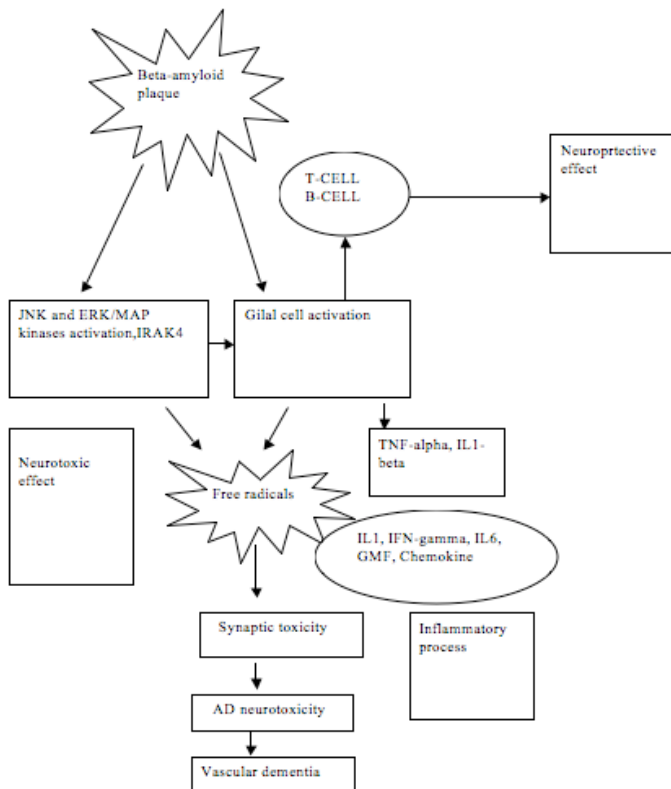
Fig.3 Role of Aβ and glial cell in pathogenesis of vascular dementia

4. Role of neurofibrillary tangles in vascular dementia

Neurofibrillary Tangles

Neurofibrillary Tangles (NFTs) are aggregates of hyperphosphorylated tau protein that are most commonly known as a primary marker of Alzheimer's disease. Their presence is also found in numerous other diseases known as tauopathies [71]. Neurofibrillary tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregation in an insoluble form [28]. The precise mechanism of tangle formation is not completely understood, and it is still controversial whether tangles are a primary causative factor in disease or play a more peripheral role [39, 40]. The cause is involved in tau binds to microtubules and assists with their formation and stabilization. However when tau is hyperphosphorylated, it is unable to bind and the microtubules become unstable and begin disintegrating [72, 74]. The unbound tau clumps together in formations called neurofibrillary tangles. More explicitly, intracellular lesions known as pretangles develop when tau is phosphorylated

excessively and on improper amino acid residues. These lesions, over time, develop into filamentous neurofibrillary tangles (NFTs) which interfere with numerous intracellular functions [61]. There has been some suggestion that the formation of NFTs does not have a causal relationship with disease. Rather that NFTs may be produced in response to a variety of conditions and may in fact be a compensatory response against oxidative stress and serves a protective function [54]. Several points are made to argue the position that NFTs are perhaps protective instead of harmful. First there appears to be a dispute as to the impact of neurofibrillary tangles on neuronal viability because some neurons containing NFTs survive for decades. Furthermore NFTs have been found in apparently healthy individuals, indicating that NFTs are not directly related to neural degeneration [65, 67]. It has been proposed that the formation of NFTs is part of a multifaced compensatory response where oxidative insult activates several kinases, which are then capable of phosphorylating tau [29]. This then prompts the early formation of NFTs, which reduce oxidative damage and prolong the function of the neuron. Traditionally believed to play a major role in neuron loss, NFTs are an early event in pathologies such as vascular dementia, and as more NFTs form, there is substantially more neuron loss [49, 50]. However, it has been shown that there is significant neuron loss before the formation of neurofibrillary tangles, and that NFTs account for only a small proportion of this neuron loss Coupled with the longevity of neurons containing NFT [54].

4. Linking role of Aβ and Tau in neurotoxicity (vascular dementia)

In this pathway in Aβ-induced neurodegeneration extracellular Aβ induces increased intraneuronal calcium through several different mechanisms, including those represented in this summary [22]. Calpain activation is linked to both N- and

C-terminal tau cleavage and the activation of tau kinases. Caspase-cleaved tau is more likely to become aggregated and highly phosphorylated, all or some of which may result in the induction of neuronal death pathways, including apoptosis-associated caspase activation [22, 23].
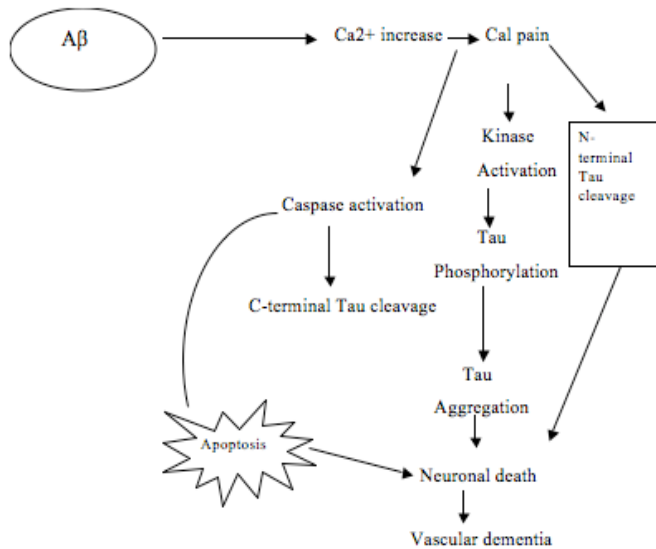

Fig.3 Aβ and Tau induced vascular dementia

5. Role of Caspase in vascular dementia

The caspases is a large quaternary protein structure formed in the process of apoptosis. Its formation is triggered by the release of cytochrome c from the mitochondria in response to an internal (intrinsic) or external (extrinsic) cell death stimulus. Caspases, or cysteine-aspartic proteases or cysteine-dependent aspartate-directed proteases are a family of cysteine proteases that play essential roles in apoptosis (programmed cell death), necrosis, and inflammation [18, 19]. Caspases are essential in cells for apoptosis, or programmed cell death, in development and most other stages of adult life, and have been termed "executioner" proteins for their roles in the cell [22]. Some caspases are also required in the immune system for the maturation of lymphocytes. Failure of apoptosis is one of the main contributions to tumour development and autoimmune diseases; coupled with the unwanted apoptosis that occurs with ischemia or vascular dementia [27, 28]. There are two types of apoptotic caspases: initiator (apical) caspases and effector (executioner) caspases. Initiator caspases (e.g., CASPASE2,CASPASE8,CASPASE9, and CASP10) cleave inactive pro-forms of effector caspases, thereby activating them. Effector caspases (e.g., CASPASE3,CASPASE6,CASPASE7) in turn cleave other protein substrates within the cell, to trigger the apoptotic process [29]. The initiation of this cascade reaction is regulated by Caspase inhibitors. Caspases are regulated at a post-translational level, ensuring that they can be rapidly activated. They are first synthesized as inactive pro-caspases that consist of a prodomain, a small subunit and a large subunit. Initiator caspases possess a longer prodomain than the effector caspases, whose prodomain is very small [35]. The prodomain of the initiator caspases contain domains such as a CARD domain (e.g., caspases-2 and caspase-9) or a death effector domain (DED) (caspases-8 and caspase-10) that enables the caspases to interact with other molecules that regulate their activation [23]. These molecules respond to stimuli that cause the clustering of the initiator caspases. Such clustering allows them to activate automatically, so that they can proceed to activate the effector caspases. The involvement of caspases in VaD began with studies examining the mechanism responsible for the neuronal cell death associated with this disease [17, 18]. Many of these early studies consisted of in situ detection of fragmented DNA utilizing terminal deoxyuridine triphosphate nick end-labeling (TUNEL) techniques. The presumption being that during apoptosis, DNA is cleaved into a characteristic profile of fragments, which can be detected using TUNEL techniques. One approach to detect apoptosis is to follow the activation caspases or their protein fragments following caspase cleavage [12, 13]. Caspases are indispensable for the execution of apoptosis, being responsible for the phenotypic characteristics of apoptosis following the cleavage of critical cellular proteins. Because caspases are specific in that they cleave only after aspartic residues, antibodies can be

designed that are based upon consensus Caspase-cleavage sites and therefore are highly specific for either the targeted Caspase or a specific protein substrate [23]. It was demonstrated that the amyloid precursor protein (APP) is a substrate for caspase-3-mediated cleavage, which may contribute to Aβ formation, synaptic loss, and the behavioral changes associated with dementia [11]. The Caspase cleavage of fodrin in the VaD brain as well as the activation of specific initiator and executioner Caspases including caspase-3,-6,-8,and-9. Collectively, these are firmly established the activation of apoptotic pathways during the course of the disease progression in VaD. Moreover, caspases may be playing a proximal role in the disease mechanisms underlying VaD including promoting Aβ formation as well as linking plaques to NFTs. Caspase 9 exists as a zymogen in the cytosol and is thought to be found at 20 nM in cells [33]. Though it is known that the zymogen does not need to be cleaved in order to become active, the activity of procaspase-9 may increase significantly once cleaved. The first hypothesis is that the apoptosome provides a location for the dimerization of two caspase 9 molecules before cleavage. The second is that cleavage takes place while caspase 9 is still in its monomeric form. In each case, caspase 9 activation leads to the activation of a full caspase cascade and subsequent cell death. It has been suggested that the evolutionary reason for the multimeric protein complex activating the caspase cascade is to ensure trace amounts of cytochrome c do not accidentally cause apoptosis [28].

Discussion

Vascular dementia is common form of neurological disorder with symptoms of dementia due to neuronal loss in the CNS. There are number of mediators like TNF-α, IL-1, 1L-6, cytokins, ROS and some excitotoxic neurotransmitters plays crucial role of development of vascular dementia. The prevalence and severity of this disease increase day by day because there is no or very less availability of potentially targeting agent. Recently various drugs are approved by FDA for the treatment of vascular dementia but they were less effective and have high toxic effect. Also these drugs provide symptomatical

relief and hence further studies are required to achieve good therapeutic agent to prevent neurodegeneration and loss of memory (dementia) by targeting these molecular mechanisms.
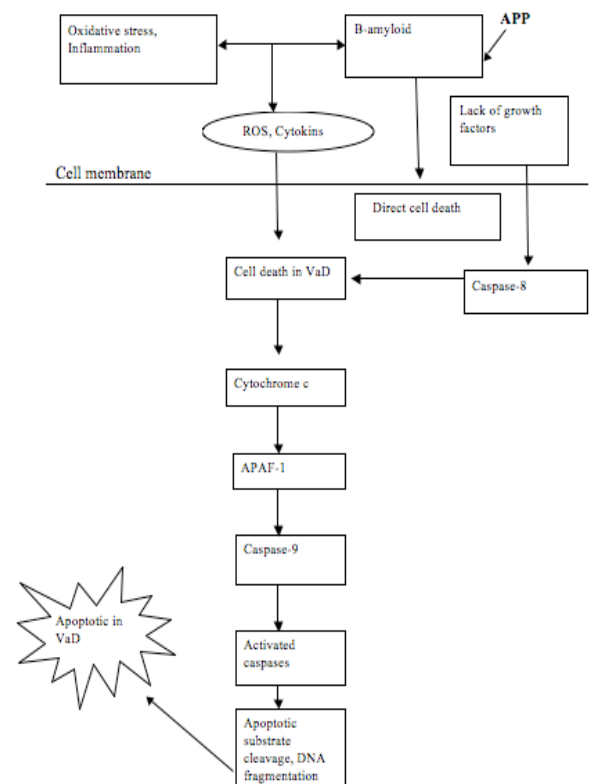

Fig4. Role of Caspase in Vascular dementia

References

1. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in vasculars dementia. Acta Neuropathol. 2009; 118:103–113.

2. Gorelick, P. B., A. Scuteri, et al. "Vascular contributions tocognitive impairment and dementia a statement for healthcareprofessionals from the American Heart Association/American Stroke Association." Stroke. 2011; 42(9): 2672-2713.

3. Brown WR, Moody DM, Thore CR, Anstrom JA, Challa VR. Microvascular changes in the white mater in dementia. J Neurol Sci. 2009; 283:28–31.

4. Van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences:

Rotterdam Scan study. Stroke. 2008; 39:2712–2719.

5. Román, G. C. "Vascular dementia may be the most common form of dementia in the elderly." Journal of the neurological sciences. 2002; 203: 7- 10.

6. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke. 1997; 28:652–659.

7. Steyn, K. and J. M. Fourie. "The Heart and Stroke Foundation South Africa." Media Data Document. Cape Town: Department of Medicine, University of Cape Town, and Chronic Diseases of Lifestyle Unit, 2009.

8. Erkinjuntti, T., D. Inzitari, et al. Research criteria for subcortical vascularementia in clinical trials, Springer, 2000.

9. Black, S., F. Gao, et al. "Understanding white matter disease imaging and pathological correlations in vascular cognitive impairment." Stroke. 2009; 40 (3 suppl 1): S48-S52

10. Kivipelto, M., T. Ngandu, et al. "Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease." Archives of neurology. 2005;62(10): 1556-1560.

11. Hamer, M. and Y. Chida. "Physical activity and risk of neurodegenerativedisease: a systematic review of prospective evidence." Psychological medicine. 2009; 39(01): 3-11.

12. Hassan A, Hunt BJ, O'Sullivan M, et al. Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. Brain. 2003; 126:424–432.

13. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease systematic review and meta-analysis. Neurobiol Aging. 2009; 30:337–352.

14. Bleau, A.-M., D. Hambardzumyan, et al. "PTEN/PI3K/Akt pathway regulates the side population phenotype and ABCG2 activity in glioma tumor stem-like cells." Cell stem cell. 2009; 4(3): 226-235.

15. Feigin, V., Y. Ratnasabapathy, et al. "Does blood pressure lowering treatment prevents dementia or cognitive decline in patients with cardiovascular and cerebrovascular disease?" Journal of the neurological sciences. 2005; 229: 151-155.

16. Butters, M. A., J. B. Young, et al. "Pathways linking late-life depression to persistent cognitive impairment and dementia." Dialogues in clinical neuroscience. 2008; 10(3): 345.

17. Au R, Massaro JM, Wolf PA, et al. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. Arch Neurol. 2006; 63:246–250.

18. De Caterina R, Massaro M, Scoditti E, Annunziata Carluccio M: Pharmacological modulation of vascular inflammation in atherothrombosis. Ann NY Acad Sci.2010, 1207:23-31.

19. Gimbrone MA Jr: Vascular endothelium, hemodynamic forces and atherogenesis.Am J Pathol. 1999; 155:1-5.

20. Luchsinger, J., C. Reitz, et al. "Aggregation of vascular risk factors and risk of incident Alzheimer disease." Neurology. 2005; 65(4): 545-551.

21. Ferri, C. P., M. Prince, et al. "Global prevalence of dementia: a Delphi consensus study." The Lancet. 2006; 366(9503): 2112-2117.

22. Bermejo-Pareja, F., E. D. Louis, et al. "Risk of incident dementia in essential tremor: A population-based study." Movement Disorders. 2007; 22(11):1573-1580.

23. Tardito, D., J. Perez, et al. (2006). "Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressants: a critical overview." Pharmacological reviews. 58(1): 115-134.

24. Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network onAtherothrombosis: Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009, 54:2129-2138.

25. Pober JS, Min W, Bradley JR: Mechanisms of endothelial dysfunction, injury and death. Annu Rev Pathol. 2009, 4:71-95.

26. Warner-Schmidt, J. L. and R. S. Duman. "Hippocampal neurogenesis:opposing effects of stress and antidepressant treatment." Hippocampus. 2006; 16(3): 239-249.

27. Stapelberg, N., D. Neumann, et al. "From Physiome to Pathome: A Systems Biology Model of Major Depressive Disorder and the Psycho-Immune-Neuroendocrine Network." Current Psychiatry Reviews. 2015; 11(1): 32- 62.

28. Videbech, P. and B. Ravnkilde. "Hippocampal volume and depression: a meta- analysis of MRI studies." American Journal of Psychiatry. 2004; 161(11): 1957-1966.

29. Dantzer, R., J. C. O'Connor, et al. "From inflammation to sickness ,depression: when the immune system subjugates the brain." Nature reviews neuroscience. 2008; 9(1): 46-56.

30. Barat, P., J.-B. Corcuff, et al. "Associations of glucocorticoid receptor and corticosteroid-binding globulin gene polymorphisms on fat

mass and fat mass distribution in prepubertal obese children." Journal of physiology and biochemistry. 2008; 68(4): 645-650.

31.Andjelkovic AV, Pachter JS: Central nervous system endothelium in neuroinflammatory, neuroinfectious, and neurodegenerative disease. J Neurosci Res. 1998, 51:423-430

32.Lawrence Robison, Jocelyn Block, M.A., Melinda Smith, M.A., and Jeanne Segal, Ph.D. Last updated: February 2015.

33.Warner-Schmidt, J. L. and R. S. Duman. "Hippocampal neurogenesis:opposing effects of stress and antidepressant treatment." Hippocampus. 2006; 16(3): 239-249.

34.Stapelberg, N., D. Neumann, et al. "From Physiome to Pathome: A Systems Biology Model of Major Depressive Disorder and the Psycho- Immune-Neuroendocrine Network." Current Psychiatry Reviews. 2015; 11(1): 32-62.

35.C. Iadecola, J. Anrather The immunology of stroke: from mechanisms to translationNat. Med. 2011; (17): 796–808

36.J.A. Schneider, P.A. Boyle, Z. Arvanitakis, J.L. Bienias, D.A. Bennett Subcortical infarcts, Alzheimer's disease pathology, and memory function in older personz Ann. Neurol. 2007; (62): 59–66.

37.J.B. Toledo, S.E. Arnold, K. Raible, J. Brettschneider, S.X. Xie, M. Grossman, S.E. Monsell, W.A. Kukull, J.Q. Trojanowski,Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre, Brain. 2013; (136): 2697–2706.

38.De Silva, T. M. and F. M. Faraci. "Effects of angiotensin II on the cerebral circulation: role of oxidative stress." Frontiers in physiology. 2012; (3).

39.Garrido, A. M. and K. K. Griendling. "NADPH oxidases and angiotensin IIreceptor signaling." Molecular and cellular endocrinology. 2009; 302(2): 148- 158.

40.Kaukinen, A. "Molecular Characterization of Fibrotic Scarring in Kidneys with Congenital Nephrotic Syndrome of the Finnish type, 2010.

41.Girouard, H., L. Park, et al. "Angiotensin II attenuates endothelium- dependent responses in the cerebral microcirculation through nox-2–derived radicals." Arteriosclerosis, thrombosis, and vascular biology. 2006; 26(4): 826- 832.

42.B.V. Zlokovic Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders, Nat. Rev. Neurosci. 2011; (12): 723–738.

43.Bruce AJ, Boling W, Kindy MS, Peschon J, Kraener PJ, Carpenter MK, Holtsberg FW, Mattson MP Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. Nat Med. 1996; (2):788–794.

44.Francis JW, Von Visger J, Markelonis GJ, Oh TH Neuroglial responses to the dopaminergic neurotoxicant, 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine in mouse striatum. Neurotoxicol Teratol. 1995; (17):7–12.

45.Lassègue, B. and K. K. Griendling. "NADPH oxidases: functions and pathologies in the vasculature." Arteriosclerosis, thrombosis, and vascular biology. 2010; 30(4): 653-661.

46.Kazama, K., J. Anrather, et al. "Angiotensin II impairs neurovascular coupling in neocortex through NADPH oxidase–derived radicals." Circulation research. 2004; 95(10): 1019-1026.

47.Toda, N. "Age-related changes in endothelial function and blood flow regulation." Pharmacology & therapeutics. 2012; 133(2): 159-176.

48.Chrissobolis, S. and F. M. Faraci. "The role of oxidative stress and NADPHoxidase in cerebrovascular disease." Trends in molecular medicine. 2008;14(11): 495-502.

49.Tong, X.-K., C. Lecrux, et al. "Age-dependent rescue by simvastatin of Alzheimer's disease cerebrovascular and memory deficits." The Journal of Neuroscience. 2012; 32(14): 4705-4715.

50.Sriram K, Benkovic SA, Miller DB, O'Callaghan JP Obesity exacerbates chemically induced neurodegeneration. Neuroscience. 2002; 115:1335–1346.

51.Sriram K, Matheson JM, Benkovic SA, Miller DB, Luster MI, O'Callaghan JP Deficiency of TNF receptors suppresses microglial activation and alters thesceptibility of brain regions to MPTP-induced neurotoxicity: role of TNF-α FASEB J. 2006a; 20:670–682

52.Sriram K, Miller DB, O'Callaghan JP Minocycline attenuates microglialn activation but fails to mitigate striatal dopaminergic neurotoxicity: role of tumor necrosis factor-! J Neurochem. 2006b; 93:706–718.

53.Kisseleva, T. and D. A. Brenner. "Role of hepatic stellate cells in fibrogenesisand the reversal of fibrosis." Journal of gastroenterology and hepatology. 2007 22(s1): S73-S78.

54.Inoue, R., L. J. Jensen, et al. "Transient receptor potential channels in cardiovascular function and disease." Circulation research. 2006; 99(2): 119-131.

55.Yoshikawa, T. and H. Kanazawa. "Cellular Signaling Crosstalk between Multiple Receptors for Investigation of Pathophysiology in Multifactorial Diseases-What is Clinically-Relevant Crosstalk?" Current medicinal chemistry. 2013; 20(9): 1091-1102.

56. Guilluy, C., J. Brégeon, et al. "The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure."Nature medicine. 2010; 16(2): 183-190.

57. Raftopoulou, M. and A. Hall. "Cell migration: Rho GTPases lead the way." Developmental biology. 2004; 265(1): 23-32.

58.Seilhean D, Kobayashi K, He Y, Uchihara T, Rosenblum O, Katlama C, Bricaire F, Duyckaerts C, Hauw JJ Tumor necrosis factor-alpha, microglia and astrocytes in AIDS dementia com- plex. Acta Neuropathol (Berl). 1997; 93:508– 517.

59.McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. Ann N Y Acad Sci. 2004; 1035:104–116.

60.Triggle, C. R., S. M. Samuel, et al. "The endothelium: influencing vascularsmooth muscle in many ways." Canadian journal of physiology and pharmacology. 2009; 90(6): 713-738.

61.Miller, A. A., G. R. Drummond, et al. "Novel isoforms of NADPH- oxidase in cerebral vascular control." Pharmacology & therapeutics. 2006; 111(3): 928- 948.

62.Lecrux, C. and E. Hamel. "The neurovascular unit in brain function and disease." Acta Physiologica. 2011; 203(1): 47-59.

63.Gordon, G. R., S. J. Mulligan, et al. "Astrocyte control of the cerebrovasculature." Glia. 2007; 55(12): 1214-1221.

64.Altenhöfer, S., K. A. Radermacher, et al. "Evolution of NADPH oxidase inhibitors: selectivity and mechanisms for target engagement." Antioxidants & redox signaling, 2014.

65.Kuwashima J, Nakamura K, Fujitani B, Kadokawa T, Yoshida K, Shimizu M. Relationship between cerebral energy failure and free fatty acid accumulation following prolonged brain ischemia. Jpn J Pharmacol. 1978; 28:277–287.

66.Murphy EJ. Brain fixation for analysis of brain lipid-mediators of signal transduction and brain eicosanoids requires head-focused microwave irradiation: an historical perspective. Prostaglandins Other Lipid Mediat. 2010; 91:63–67.

67.Selnes, O. A. and H. V. Vinters (2006). "Vascular cognitive impairment." Nature Clinical Practice Neurology. 2(10): 538-547

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.