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Recent Advance of Enzyme Targets for the Management of Vascular Dementia

Arunachalam Muthuraman, Narahari Rishitha and Johurul Islam

Abstract

The basic understanding of vascular dementia (VaD) and their molecular mechanisms are a too complex phenomenon. VaD associated neurodegeneration and cognitive impairment are due to multiple complications of the neurovascular system. The progress of VaD is due to the central and/or peripheral pathophysiological process of the neurovascular system. There are limited nootropic agents are employed for the treatment of VaD. Moreover, the explored nootropic agents act on multiple targets such as receptors, enzymes, ion channel, free radicals, cytokines, chemokines, and apoptotic proteins. However, the enzyme targets, especially acetylcholinesterase inhibitors played a crucial role in the management of cognitive disorders. The pathogenesis of VaD is involved in the vascular complication and neurodegenerative process. Hence, the enzymatic regulation of neurovascular complication is expected to prevent the VaD. The present chapter attempts to explore the recent advancement of enzyme targets for the management of VaD.

Keywords: cognitive dysfunction, enzymes, memory, neurodegeneration, neurovascular complication, vascular dementia

1. Introduction

Vascular dementia (VaD) is one of the leading factors for the changes in quality of life. It is declining the thinking ability [1]. The major etiology in the pathogenesis of VaD is blockage of cerebral blood vessels and/or reduction of regional and global cerebral blood flow [2]. This leads to depriving the brain cells for vital oxygen and energy by rising of free radicals; reduction of endogenous anti-oxidants and their regulatory enzymes [3]. The aging is another factor to develop neurovascular complications [4]. The developing country like India faces the serious complication of vascular dementia. India has more than 75 million populations older (above 60 years) [5]. This age group; dramatically grow 7.5% of the population in every decade [6]. Therefore, demanding care for older people is growing day by day. The certain neurological disorders mainly occur in old age like dementia and Alzheimer's disease (AD); however, the specialized medicines and improvements quality of life remains limited and challengeable [7]. Furthermore, VaD is mainly due to the various changes in vascular compartments in the brain. It is classified as cortical vascular dementia; subcortical ischemic dementia; strategic-infarct dementia;

hypoperfusion dementia; hemorrhagic dementia; and dementias of specific pathology of cerebral artery [8]. The primary hallmark of the VaD is the development of cognitive deficits and impairment of functional abilities. The more specific diagnostic criteria for VaD described by Diagnostic Manual of Mental Disorders, 4th edition (DSM-IV) criteria [9]; and National Institute of Neurological Disorders and Stroke—Association International pour le Recherche at L'Enseignement en Neurosciences (NINDS-AIREN) criteria [10]. The DSM-IV criteria have good sensitivity, but low specificity. Whereas the NINDS-AIREN criteria are the most specific to all available criteria and most commonly used in clinical research [11]. The clinical features of VaD are determined by the size, location, and type of cerebral damage. The classical clinical features of VaD are the abrupt onset of memory, stepwise deterioration of mental function, fluctuating learning course, abnormalities of the motor and sensory response, gait changes and development of urinary incontinence [11].

Currently, the nootropic agents are used to treat the VaD [12]. Thus, the prescription of nootropic agents such as central nervous system (CNS) stimulants (amphetamine, methylphenidate, caffeine and nicotine) [12]; Racetams [positive allosteric modulators of AMPA receptors and cholinergic systems such as piracetam, oxiracetam and aniracetam] [13, 14]; and miscellaneous such as L-theanine, tolcapone, levodopa, atomoxetine, *Panax ginseng*, *Ginkgo biloba*, *Salvia officinalis* [15], omega-3 fatty acids, folate, vitamin B₆, B₁₂, and E [16, 17]; pramipexole, guanfacine clonidine, and fexofenadine are documented to produce the ameliorative effect in neurocognitive disorders like vascular dementia [18, 19]. However, it produces the potential adverse effects and chronic usage it shown less efficacy [20]. Various nootropic agents are acts via multiple cellular targets like receptors, enzymes, ion channel, free radicals, cytokines, chemokines and apoptotic proteins [21]. However, the enzyme targets are shown to produce the better beneficial effects in neurocognitive disorders like acetylcholinesterase inhibitors carbamates (physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, and rivastigmine) [22, 23]; phenanthrene derivatives (galantamine) [24]; donepezil; tacrine, edrophonium and huperzine A [25]. Therefore, this book chapter is focused to explore the role of enzymes in the pathogenesis of VaD and also discussed the recent advancement of enzymes targets based medicines for the management of VaD disorders.

2. Risk factors of vascular dementia

Globally, the aging peoples are suffering from dementia and AD and increase the burden to maintain the quality of life. The effective medicines for the treatment of VaD are not available and conventional nootropic medicines are relived the VaD symptomatically [26]. The factor medication for the pathogenesis of VaD is reducing the risk of cognitive decline effects. The main modifiable risk factors for VaD are lack of exercise, smoking, hypertension, obesity, diabetes mellitus, and chronic depression. The maintenance of this modifiable risk factors are supporting to prevents the pathogenesis of VaD and enhances the cognitive reserve function & quality of healthy life [27].

3. Characteristic features of VaD

The main characteristic features of VaD is described the problems of reasoning, planning, judgment, memory and thought processes. It occurs by damage central nervous system; and lack of cerebral blood circulation; and depriving of

the brain of vital oxygen and nutrients. Other than hyperglycemia, hypertension, hyper-lipidemia, and smoking; certain diseases also cause VaD like heart disease and stroke [28]. In the acute stage, confusion, trouble in attention; reduction of thinking ability; analyzing the ability of situation; deciding ability; restlessness; agitation; abnormal gait posture; frequent urination and/or inability to control the passing of urine; depression; and apathy. This characteristic feature of VaD develops the gradual manner like AD. The two main characteristic features are important for the pathogenesis of neurovascular disorders like VaD; one is arterial infarction (stroke) associated blocking of cerebral artery [28]. Some strokes are not producing noticeable symptoms of VaD. Whereas, it enhances the risk of VaD; and it is called multi-infarct dementia. Another feature of VaD is the chronic narrowness of cerebral blood vessels. It occurs by long-term damage of brain blood vessels by aging, high blood pressure, abnormal cholesterol deposition in the cerebral blood vessels, diabetes and brain hemorrhage [29]. These features are changes the wear and tear principles of cerebral blood vessels leads to cause the VaD.

4. Enzymes as a target for VaD

Various enzymes are identified in the regulation of neurovascular peptide action and it can prevent the cognitive disorders. Mainly drug target is focused on the receptors; ion channels; and nuclear proteins. There are limited drugs are explored in the enzymes based drug therapy for the neurovascular disorders [30]. Enzyme targeted medicines effectively prevent the various disorders such as inflammation (cyclooxygenase inhibitor); peptic ulcer (proton pump inhibitor); heart failure (sodium-potassium ATPase inhibitor); hypertension (angiotensin-converting enzyme inhibitor); depression (monoamino oxidase inhibitor); including memory disorder (acetylcholinesterase inhibitor). This chapter will open the “Pandora’s box” for the newer drug discovery for the treatment of VaD via enzyme inhibitors and modulators.

4.1 Acetylcholinesterase

Acetylcholinesterase (AChE; EC 3.1.1.7) also called as acetyl hydrolase. It belongs to carboxyl esterase family of enzymes. It predominantly acts on multiple organ systems including central as well as the peripheral nervous system [31]. The primary action of AChE is a breakdown of the acetylcholine to choline esters. In addition, it acts as neurotransmitters and alters the neuromuscular junctions and synaptic junctions. In addition, the central cholinergic system is plays a key role in the neuromodulatory action; vasomotor control; cerebral circulation of blood; and cognitive function. The basal prosencephalon and routes of their projections are the main areas for the cognitive function [32]. The vascular lesion of this area alters the cholinergic neuronal pathways via acetylcholinesterase and cholinergic neurotransmitter action. The denervation of this cholinergic neuron plays a role in the development of cholinergic hypofunction and vascular dysfunction. Which leads to enhance the VaD associated cognitive dysfunction [32]. The administration of cholinesterase inhibitors like donepezil, galantamine and rivastigmine are symptomatically relieved the symptoms of VaD in human [33]. Similarly, all three agents are shown beneficial effects in mild to the moderate condition of Alzheimer disease (AD) type of VaD. Even though, FDA has not approved the cholinesterase inhibitors for the treatment of advanced stages of the AD; due to lack of efficacy and tolerability. Hence, some of the research reports suggest that cholinesterase inhibitors might

be useful for the other types of dementia like vascular dementia and dementia with Lewy bodies.

4.2 Amyloid- β -peptide alcohol dehydrogenase

ABAD (EC: 1.1.1.178) enzymes also belong from oxidoreductase enzyme. This alcohol dehydrogenase is activated by amyloid- β peptide and it affects cellular functions. The extracellular amyloid- β peptide is interacting with cell surface receptors and its trigger the intracellular signaling cascades. In addition, the amyloid- β peptide is interacting with specialized mitochondrial enzyme i.e., amyloid- β peptide-binding alcohol dehydrogenase (ABAD) [34]. The binding properties of the amyloid- β peptide to ABAD have altered the metabolic properties of the neuronal cell, and promotes mitochondrial free radicals synthesis via modulating the electron transport chain [35]. The activation of ABAD is required dinucleotide cofactor i.e., nicotinamide adenine dinucleotide (NADH). The over-activation of ABAD enhance the amyloid- β rich environment leads to accelerates the cell stress leads to raising the levels of 4-hydroxynonenal-lysine; malondialdehyde-lysine; and induction of DNA fragmentation of the neurovascular system. In addition, ABAD induces the utilization of ketone bodies by neurovascular cells by promoting the conversion of acetyl-CoA to tricarboxylic acid cycle. This reaction also enhances the nutritional and/or metabolic stress [36]. The ABAD mutated (upregulated) transgenic mice are shown the amyloid- β peptide-rich environment leads to accelerates the spatial learning and memory impairment via cellular oxidative stress [37]. Hence the A β and their target enzymes ABAD are contributed in the pathogenesis of neurovascular disorders including VaD. Therefore, the authors review the evidence that the prevention of A β binding to ABAD is a drug target for the treatment of AD. Therefore, the ABAD can be considered as a newer target for the attenuation of VaD.

4.3 Angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE; EC: 3.4.17.23) is one of the families of hydrolase enzyme. ACE is a major component for the renin-angiotensin system (RAS). It plays a key role in the pathogenesis of blood pressure. ACE converts the angiotensin I (AT-I) to angiotensin II (AT-II). AT-II peptide is a potent endogenous vasoconstrictor. In addition, AT-II peptide and their receptor also play a various pathophysiological action on the central nervous system [38]. The brain-derived ACE has a role in the alteration of cerebral hemodynamics and execution of cognitive functions. Further, some literature revealed that anti-hypertensive medicines such as ACE inhibitors are shown the improvement of cognitive function via reduction of neurovascular damage. The inhibitor of centrally acting ACE enzymes like captopril, fosinopril, lisinopril, prinivil, perindopril, ramipril, andtrandolapril is slow down the cognitive deterioration in human [39].

Furthermore, ACE interferes with bradykinin pathway in lung system and epithelial cells of the renal tissue. Currently, ACE is identified for the progress of neurodegenerative process via alteration of amyloid- β peptide metabolic and catabolic events. The treatment of ACE inhibitors is documented to produce the neuroprotection and prevention of neurodegenerative process [40]. The administration of central acting ACE inhibitor i.e., captopril and perindopril are produced the ameliorative effect in late-onset AD type of VaD. Moreover, another ACE inhibitors i.e., enalapril and ramipril are also controlled the dementia-related cognitive dysfunction [41]. Therefore, the ACE enzymes are playing a key target for the discovery of newer ACE inhibitors for VaD treatment.

4.4 Endothelin-converting enzyme

Endothelin-converting enzyme (ECE) belongs from hydrolase family of enzyme and it is encoded by the ECE gene in human. The function of ECE is involved in the proteolysis process of endothelin peptides. There are three biologically active ECE are identified i.e., ECE-1; ECE-2; and ECE-3. The ECE-1 are catalyzed the biologically active endothelin-1 (ET₁); endothelin-2 (ET₁); and endothelin-3 (ET₁) peptides. The ECE-1 is primarily originated from endothelial cells; whereas, ECE-2 is originated from neuronal cells. Both ECEs have induced the ET-1 peptide production and cleavage the amyloid- β peptides [42]. The treatment of amyloid- β_{40} and amyloid- β_{42} peptides enhances the ECE-2 gene expression and release of ET-1 in neurovascular tissue. In addition, the endogenous superoxide dismutase prevents the amyloid- β_{40} induced release of ET-1. In AD patients, ECE₁ induces the production of endothelin-1; and free radical is enhancing the cerebral vasoconstriction and reduction of cerebral blood flow. The chronic reduction of cerebral blood flow is one of the hallmarks in the pathogenesis of VaD [43]. The ECE hydrolyzes the bioactive peptides like bradykinin, neurotensin, substance P and insulin B chain. In addition, the over-activation of ECEs are involved in the alteration of amyloid- β degradation. The ECE are altered the neurovascular function of various brain areas such as cerebral cortex, hippocampus, amygdala, basal forebrain nuclei, diencephalon, brain stem, cerebellar hemisphere including hippocampus neurons. The clearance of amyloid β (A β) occurs by three major vasopeptidases i.e., neprilysin; ECE-1 and ECE-2. This clearance of amyloid β reactions occur by time; concentration and cellular environment dependent manner. And it accelerates the cellular metalloproteases enzymes leads to alter the vascular function and enhances the pathogenesis of VaD [44].

In addition, the non-selective dual endothelin-A (ET-A) and ET-B receptor antagonist i.e., bosentan ameliorates diabetes induced vascular endothelial dysfunction and vascular dementia in rats [45]. Similarly, it also attenuates the hyperhomocysteinemia, β -amyloid and renovascular hypertension-induced vascular dementia in rats. Further, the administration of selective endothelin ET-A receptor antagonist i.e., ambrisentan attenuates the L-methionine-induced vascular dementia in rats [46]. ECEs inhibitors can control the accumulation of ET-1 peptide and activation of ET receptors. Therefore, ECE regulators, especially ECE-1 can be a key target for the management of VaD.

4.5 Histone deacetylase

Histone deacetylase (HDAC; EC: 3.5.1.98) is belonging from the hydrolases type of enzymes. HDAC removes the acetyl groups ($O = C - CH_3$) from ϵ -N-acetyl lysine amino acid of the histone proteins. And, it makes the tight wrapping of DNA to histone proteins [47]. This process supports the regulation of DNA expression via the cyclic action of acetylation and de-acetylation events. Histone acetyltransferase is opposite the histone deacetylase action. In addition, lysine deacetylases (KDAC) enzymes are similar to that of HDAC action; but it also produces the non-histone protein-mediated DNA expression actions. The primary action of HDAC action is a modification of histone tails via modification of lysine and arginine amino acids. These changes make the positive charges environment on histone tails and interact negatively charged phosphate groups of DNA backbone [48]. Acetylation process is neutralizing the positive charges of the histone tail leads to decreases the DNA interactions. In this case, histone proteins allow the chromatin expansion; permits the gene transcription. In a paradox, HDAC opposite this all reaction sequences. In a

normal cell, HDAC is regulated the cellular processes via cell growth; cellular apoptosis; and cell cycle events. In pathological conditions, it stimulates the cancer cell growth; and activates the chronic myeloid leukemia progress. The hyperacetylation of chromatin is causing the abnormal transcription process [49].

There are 18 numbers of HDACs are identified in human i.e., HDAC₁ to HDAC₁₈. It is further divided into four classes i.e., class I: Rpd3-like proteins (HDAC₁₋₃; and HDAC₈); class II: Hda1-like proteins (HDAC₄₋₇; HDAC₉; and HDAC₁₀); class III: Sir2-like proteins (SIRT₁₋₇); and class IV protein (HDAC₁₁) [50]. HDAC inhibitor-like valproic acid is used for psychiatric disorders including epileptic disorders. Another, HDAC inhibitors *i.e.*, vorinostat and romidepsin are approved for the treatment of cutaneous T cell lymphoma [51]. Trichostatin A (potent HDAC inhibitors) are used for neurovascular disorders like stroke; AD; and VaD. The non-selective inhibitor of HDACs i.e., sodium butyrate attenuates the heavy metal i.e., arsenic metal; and streptozotocin-induced endothelial dysfunction and VaD in rats [52]. Currently, the administration of sodium butyrate also ameliorates the ischemia-induced vascular dysfunction in aged female rats [53]. Various HDAC inhibitors are documented to produce the neuroprotection against multiple and variable type of brain injury such agents are suberoylanilide hydroxamic acid (SAHA); hydroxamic acid derivatives (ITF2357); valproic acid (VPA); trichostatin A (TSA); sodium 4-phenylbutyrate (4-PBA); 4-dimethylamino-N-[5-(2-mercaptoacetyl-amino)pentyl]benzamide (DMA) [54]. However, the effect of these agents in the management

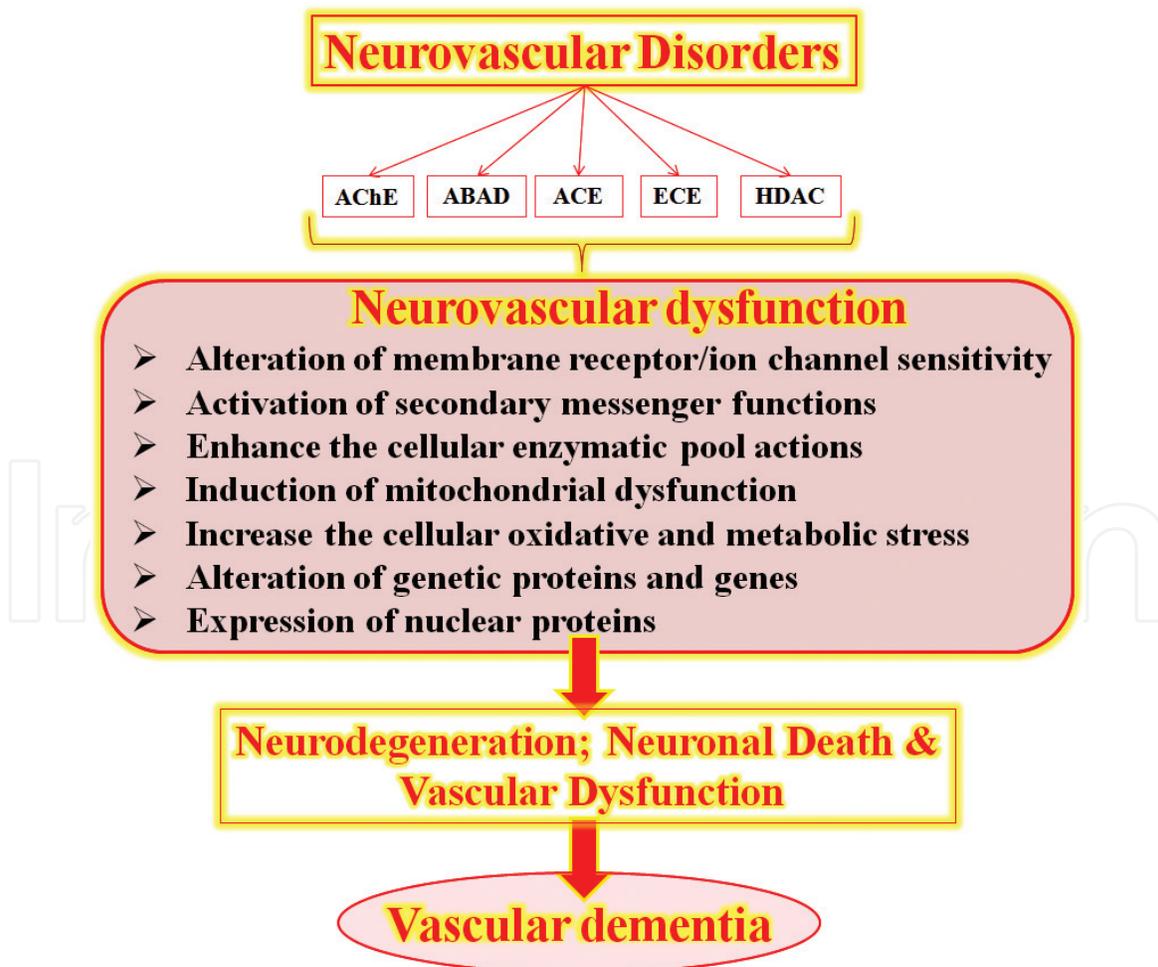


Figure 1.

This illustration revealed that, the role of neurovascular enzyme alteration for the alteration neurovascular dysfunction; neurodegeneration; neuronal death; and vascular dysfunction associated with vascular dementia. Abbreviations: AChE, acetylcholinesterase; ABAD, amyloid- β -peptide alcohol dehydrogenase; ACE, angiotensin converting-enzyme; CART, carnitine acetyltransferase; ECE, endothelin-converting enzyme-1; NOX, nicotinamide adenine dinucleotide phosphate oxidase; and HDAC, histone deacetylases.

of VaD and endothelial dysfunction is not explored yet. HDAC inhibitors are identified as neurovascular protective agents and prevention of VaD. Hence, HDAC inhibitors need to explore in the management of VaD disorders. The role of neurovascular enzyme targets and their mechanism for the alteration neurovascular dysfunction; neurodegeneration; neuronal death; and vascular dysfunction associated vascular dementia is illustrated in **Figure 1**.

5. Future perspectives

Based on the available literature, it concluded that enzymes targets can treat the neurovascular disorders via prevention of endothelial dysfunction; neuroprotection; enhancement of neuronal plasticity; and anti-apoptotic action. In addition, these enzymes targets are also regulated the neuronal as well as vascular growth factor via epigenetic modification and controlling of pre and post-translational protein modifications. Functionally, these enzymes modulators are improved the neurocognitive functions in AD, PD, stroke conditions including VaD in animals as well as in patients. Currently, the various enzymes are identified their roles; physiological & pathological functions; involvements in the neurovascular system; identification of endogenous and exogenous substrates; and their modulators. However, the limited enzyme modulators only tested in animals. Still need more discoveries to develop the enzymes modulators for the above enzymes targets with their specificity, potency and enhanced functionality. Thus, this book chapter will help to the audience to open the “Pandora’s box” for the discovery of novel enzyme targets and modulators for the treatment of neurovascular disorders.

6. Conclusion

Based on this review of the literature, it is concluded that the pathogenesis of VaD is occurred by multiple pathophysiological events. However, literature shown that enzymes targets are contributed the development of neurovascular disorders such as VaD. The chronic progress of vascular dysfunction makes the neuronal death; neurodegeneration and cognitive impairment. This book chapter section also showed the evidence of enzymes modulators for the treatment of VaD. However, the specific modulator of this enzymes targeted action is needed to investigate in different pathophysiological conditions of VaD. Further, it also needs to study in clinically relevant animal models and in human subjects.

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