



Review

Models and mechanisms of vascular dementia

Poornima Venkat^{a,b}, Michael Chopp^{a,b}, Jieli Chen^{a,c,*}^a Neurology, Henry Ford Hospital, Detroit, MI, USA^b Physics, Oakland University, Rochester, MI, USA^c Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin Geriatrics Institute, Tianjin, China

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ABSTRACT

Vascular dementia (VaD) is the second leading form of dementia after Alzheimer's disease (AD) plaguing the elderly population. VaD is a progressive disease caused by reduced blood flow to the brain, and it affects cognitive abilities especially executive functioning. VaD is poorly understood and lacks suitable animal models, which constrain the progress on understanding the basis of the disease and developing treatments. This review article discusses VaD, its risk factors, induced cognitive disability, various animal (rodent) models of VaD, pathology, and mechanisms of VaD and treatment options.

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* Corresponding author at: Senior Staff Investigator, Henry Ford Hospital, Neurology Research, E&R Building, 3091, Detroit, MI 48202, USA. Fax: +1 313 916 1318.

E-mail addresses: pvenkat3@hfhs.org (P. Venkat), mchopp1@hfhs.org (M. Chopp), jieli@neuro.hfh.edu (J. Chen).

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Introduction

Define vascular dementia

Vascular dementia (VaD) is a progressive disease that affects cognitive abilities and is caused by reduced blood flow to the brain. VaD patients may suffer from slowed thinking, forgetfulness, depression and anxiety, disorientation, and loss of executive functions like problem solving, working memory, thinking, reasoning, judgment, planning and execution of tasks, with performance declining with increasing task complexity. VaD accounts for about 17–20% of all dementia patients making it the second leading form of dementia after Alzheimer's disease (AD), and is prevalent among the older population (Plassman et al., 2007).

VaD can be caused by a reduced cerebral blood flow supplying the brain that may or may not be associated with a stroke. VaD includes the following: multi-infarct dementia characterized by multiple small strokes, single infarct dementia caused by a single major stroke with hippocampal damage, small vessel disease (SVD) and vasculitic dementia in which patients additionally suffer from migraine like headaches caused by inflammation of blood vessels. Under-diagnosis of VaD, lack of treatment options, increasing life expectancy and a steady rise in the population suffering from its risk factors like hypertension, cardiac disease, diabetes, metabolic syndrome and stroke necessitate development of treatments for VaD; Fig. 1 summarizes VaD risk factors, subtypes and characteristic features. Since, AD and VaD can have clinically similar symptoms and may coexist in many patients; the two disorders are easily confused. Hence, it is important to clearly understand the similarities and differences between VaD and AD; these have been summarized in Table 1.

Risk of vascular dementia

Diabetes

Diabetes has been established as a risk factor for VaD (Xu et al., 2009; Peila et al., 2002; Leibson et al., 1997; Kimm et al., 2011) and is reported to almost double the risk of dementia (Ott et al., 1999). Pre-diabetes and

diabetes patients also risk a conversion of mild cognitive impairment into dementia (Xu et al., 2010). Diabetes increases the risk of VaD especially when diabetes occurred in patients during their mid life, i.e. age <65 years (Xu et al., 2009). The risk of developing VaD was higher than AD with an average dementia onset age of 76.8 years (Xu et al., 2009). The duration of diabetes and occurrence of peripheral arterial disease are also independent risk factors for dementia (Bruce et al., 2008). An autopsy based study (Sonnen et al., 2009) revealed a significant difference in patients with dementia with or without diabetes and reported that while non-diabetic dementia was found associated with greater A β deposition characteristic of AD, diabetic dementia was associated with more microvascular infarctions and neuroinflammation characteristic of VaD. Neuroimaging using CT and MRI has shown a clear association between diabetes and cerebral atrophy and lacunar infarcts (van Harten et al., 2006). The involvement of diabetes with VaD is not surprising given the knowledge that diabetes increases the risk for stroke (Idris et al., 2006; Barrett-Connor and Khaw, 1988), and lacunar infarction (You et al., 1995) and is associated with extensive vascular damage and worse outcomes post stroke (Weir et al., 1997; Megherbi et al., 2003).

Hypertension

Increasing age (>60 years) is a risk factor for hypertension (Anderson, 1999) which in turn is a potential risk factor for VaD (Kennelly et al., 2009). Middle age (mean age 54 years) hypertension can increase the risk of VaD in late age (approximately 25–30 years later) especially if untreated and can increase hippocampal atrophy (Yamada et al., 2003; Ronnema et al., 2011; Launer et al., 2000; Korf et al., 2004). The impact of hypertension on VaD can be explained by several mechanisms centering around white matter (WM) damage: WM lesions in the aging non-demented population have been associated with elevated blood pressure (BP); uncontrolled and untreated hypertension is a high risk factor for WM lesions and worsens VaD disease progression; blood brain barrier (BBB) compromise, vascular changes and silent strokes induce vascular and WM damage (Verhaaren et al., 2013). Researchers and clinical trials have reported a decreased dementia risk in patients receiving treatment for hypertension (Tzourio et al., 2003; Forette et al., 2002). While the Framingham

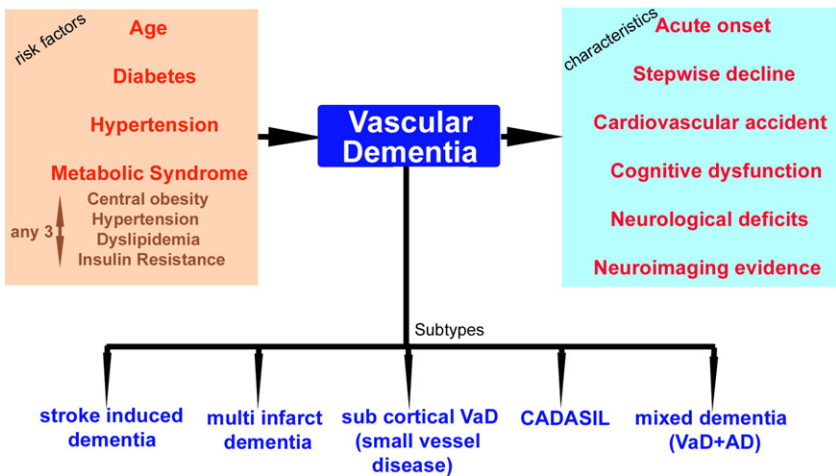


Fig. 1. Summarizes the risk factors, subtypes and characteristic features of VaD.

Table 1
Comparison between Alzheimer's Disease and Vascular Dementia.

Alzheimer's disease	Vascular dementia
Symptoms ▶ Gradual onset ▶ No neurological deficits ▶ Normal gait ▶ Language related issues during oral or written communication and vocabulary ▶ Problems with vision	▶ Sudden/gradual onset ▶ May have stroke related/stroke like deficits ▶ May have disturbed/unsteady gait ▶ Loss of bladder and/or bowel control ▶ Slurred speech ▶ Language problems (vocabulary, choice of words, confusion in communication) ▶ Loss of vision in some cases
Neurological and behavioral changes ▶ Memory impairment especially inability to learn new information or forgetting recently learnt information or events ▶ Progressive memory disorder that worsens with time	▶ Memory impairment ▶ Loss of executive function (decreased ability to plan, reason and analyze situations/problems, organize thought and behavior) ▶ May be gradual, but typically develops in a stepwise manner or sudden memory loss following a stroke (post stroke dementia) or after series of cerebrovascular accidents
<i>Common symptoms:</i> depression, disorientation, emotional instability, anxiety, mood disorder, confusion with time and place, attention deficit and general restlessness, delusions, inability to comprehend current situations, social awkwardness and withdrawal	
Diagnosis (brain imaging techniques) Computed tomography and MRI (magnetic resonance imaging) ▶ Increased beta-amyloid and tau proteins in the brain ▶ Blood brain barrier dysfunction ▶ Neuronal cell damage and death ▶ Decreased communication in the brain ▶ Brain atrophy (whole brain, entorhinal, hippocampal) ▶ Assess structural and volume changes in hippocampus and temporal lobe	CT and MRI ▶ White matter lesions ▶ Hippocampal damage ▶ Small stroke infarcts ▶ Lacunar infarcts
<i>Future direction:</i> functional MRI and PET (positron emission tomography) imaging hold promise to assess both structural and functional losses in the brain and to better diagnose dementias	
Risk factors ▶ Age ▶ Genetics ▶ Hypertension ▶ Cardiac disorders ▶ General health ▶ Diabetes	▶ Age ▶ Stroke ▶ Hypertension ▶ Cardiac disorders ▶ Atherosclerosis ▶ Diabetes ▶ Metabolic syndrome ▶ Genetics

Study (Farmer et al., 1987) has indicated a lack of influence of BP on cognitive performance, other studies have reported a lowering of systolic BP in elderly patients 3–6 years prior to the onset of dementia, and a >15 mm Hg decrease was associated with an increased risk of dementia in patients with pre-existing vascular disorders or low BP (Guo et al., 1996; Zhu et al., 1998; Qiu et al., 2004). Therefore, it is unclear if the decline in BP is a complication or side effect of dementia and if this decline in BP after high BP in mid life can be in fact used as a predictor for dementia.

Metabolic syndrome (MetS)

MetS is a combinatorial effect of at least three of several cardiovascular risk factors including abdominal/central obesity with large waistline, hypertension, dyslipidemia with high triglycerides or low high density lipoprotein (HDL) cholesterol, and insulin resistance i.e. high fasting blood glucose levels (Grundey et al., 2004 Feb 3). MetS appears to have a moderately significant effect on cognitive decline but only in patients less than 70 years (Frisardi, 2014; Siervo et al., 2014). While 65 year old MetS patients suffer from poor memory and poor executive performance (Rouch et al., 2014), in older male participants (>75 years) late life MetS could possibly induce protective effects on cognitive decline (Liu et al., 2013). MetS and in particular high triglycerides and diabetes have been indicated to increase VaD risk over 4 years in patients of age ≥ 65 years (Raffaitin et al., 2009). While the exact role of MetS in cognitive dysfunction is unclear, a decrease in cerebral blood flow (CBF) may be responsible for loss in short term/immediate memory in late middle aged MetS patients (mean age 60.4 years) especially in those who suffer from abdominal obesity and high triglycerides level (Birdsill et al., 2013). MetS increases the risk of progression from mild

cognitive impairment to dementia (Solfrizzi et al., 2011) and has been associated with increased inflammation (Solfrizzi et al., 2010; Yaffe et al., 2004).

Evaluation of cognitive dysfunction

Fig. 2 summarizes the various aspects of cognitive dysfunction that VaD patients suffer from. The clinical diagnostic criteria for VaD include NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences), ICD-10 (10th revision of the International Classification of Diseases), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) and ADDTC (Alzheimer's Disease Diagnostic and Treatment Centers), and these have been discussed previously (Lee, 2011; Wetterling et al., 1996).

In animal models, cognitive abilities can be evaluated by a battery of functional tests including but not limited to:

- 1) Odor test for olfactory learning based on animal preference for new smells (Spinetta et al., 2008);
- 2) Novel object recognition test to test short/long term (1 h–24 h) visual learning and memory based on animal bias to explore new objects (Stuart et al., 2013);
- 3) Open field test for anxiety disorders to test exploratory activity in an environment (Brown et al., 1999);
- 4) Morris water maze or Barnes maze tests for spatial and visual learning and memory with aversive motivation to assess hippocampal damage (Ohno et al., 2006);
- 5) Elevated plus maze test for anxiety related responses (Brown et al., 1999);

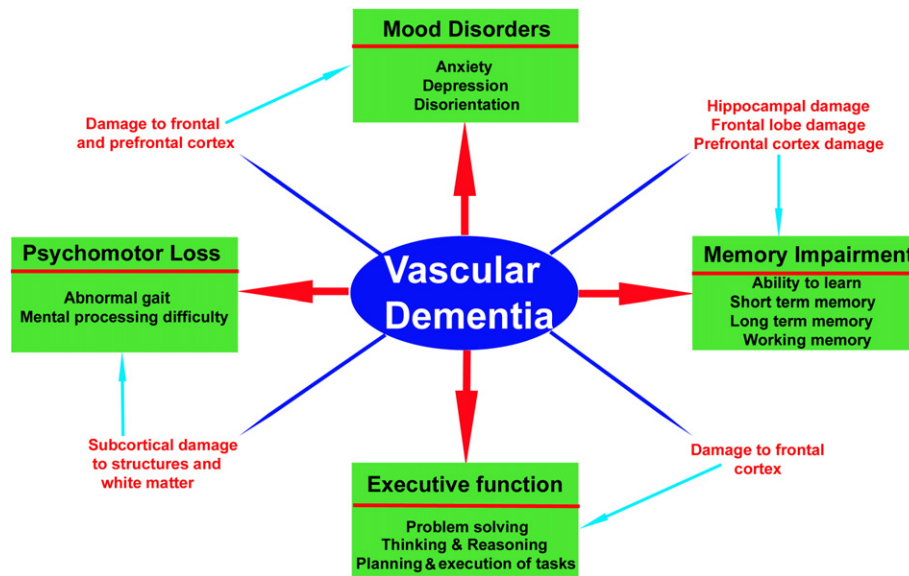


Fig. 2. Summarizes the various cognitive disabilities of VaD patients and associated brain damage.

- 6) Passive avoidance test for either short or long term memory of aversive stimulus (Ishiyama et al., 2007);
- 7) Y maze test (Weiss et al., 1998) to evaluate spontaneous alternation ability of animals.

VaD animal models

Driven mainly by the fact that there are no existing FDA approved treatment options for VaD, several research studies have aimed at developing a good VaD animal model as a first step to explore treatment options. An ideal animal model should mimic the disease conditions and outcomes as close as possible to human findings. While designing or choosing a VaD model, one should be aware that VaD can be the outcome of several pathophysiological conditions and risk factors either as stand-alone causes or in combination with each other. The common ground for most existing models is the end loss in cognitive abilities.

VaD is associated with the occurrence of a cerebrovascular incident which could be a major stroke in a region capable of compromising cognition like thalamus, frontal lobe or temporal lobe; or could result from a series of several small thromboembolic strokes often silent i.e. without clinical manifestations but accompanied with vessel damage. The most common cause of VaD is SVD (Small Vessel Disease). SVD can induce several isolated lacunar infarcts and ischemic WM lesions. In multiple infarct dementias, thromboembolic events give rise to several microinfarcts in the brain. The underlying molecular pathology in VaD is not clearly understood. Table 2 highlights the characteristics, pathophysiology and limitations of the various animal models discussed below.

Vessel occlusion models

The 2 vessel occlusion (2VO) or BCCAO (bilateral CCA occlusion) VaD animal model

The 2VO aimed to model global chronic cerebral hypoperfusion which occurs in human aging and dementia and essentially comprises the permanent occlusion of the bilateral (right and left) common carotid arteries (CCA) (Nanri and Watanabe, 1999). The pathophysiological changes in this model include WM rarefaction, WM damage, BBB disruption (mostly in WM and temporary with maximum permeability at 3 days after BCCAO), neuronal damage in the cortex and hippocampus, infarctions in the striatum of varying sizes confirmed by MRI studies, elevated inflammatory responses and gliosis primarily in the WM

(Nanri and Watanabe, 1999; Soria et al., 2013; Wakita et al., 1994; Ueno et al., 2002). Since cognitive impairment is central in dementia, several functional testing results of 2VO rats are available and have reported a higher error rate in the 8-arm radial maze test suggesting learning impairment, deficits and longer latency in the Morris water maze test, poor performance in the elevated T maze test, Y maze and object recognition test (Nanri and Watanabe, 1999; Sarti et al., 2002; Lee et al., 2014; Zhang et al., 2014a; de Bortoli et al., 2005).

The limitations of 2VO model include: this model is restricted to rats since they have a complete circle of Willis, and is not suitable for use in mouse since they lack fully developed posterior communicating arteries of the circle of Willis and can suffer from severe ischemia (Farkas et al., 2007). In rats, since the degree of ischemia and lesions may vary largely, it is important to carefully outline inclusion criteria based on lesion volume for studying VaD (Soria et al., 2013). However, some researchers have used the mouse 2VO model for studying transient global cerebral ischemia, and have found cognitive loss such as anxiety, and decreased spatial memory as well WM lesions, associated gliosis and MMP activation (Walker and Rosenberg, 2010; Lai et al., 2007). Another limiting issue involves the sudden and rapid drop in cerebral blood flow post 2VO. To circumvent this issue a recent study has proposed the use of an ameroid (Research Instruments NW, Lebanon, OR, USA) constrictor device to gradually decrease CBF in their 2 vessel gradual occlusion (2VGO) model (Kitamura et al., 2012). The 2VGO study reported selective WM injury and associated significant loss in spatial memory indicated by the Y maze test. Another effect of the 2VO is retinal and optic nerve damage, and since several cognitive tests require visual learning it is important to verify results with multiple tests (Stevens et al., 2002; Yamamoto et al., 2006). In addition, the 2VO model in Wistar rats from different vendors also induces a notable variability in hippocampal damage, as well as differing post stroke depression among rat strains (Marosi et al., 2006; Kunze et al., 2014).

4VO model

In the 4VO model, both the vertebral arteries (VA) and both the CCAs are occluded on consecutive days (Pulsinelli and Brierley, 1979). The two VA's are permanently occluded and several modifications of the model have evolved mostly adjusting the duration of CCA occlusion ranging from 15 m to permanent occlusion (Pulsinelli and Brierley, 1979; Neto et al., 2005). Occlusion of the vertebral arteries is best achieved by electrocauterization (Pulsinelli and Buchan, 1988). Various sequences of permanent vessel occlusion have been used. One report

Table 2
Summary of Animal VaD models.

Model		Model characteristics	Pathophysiology	Limitations
Vessel occlusion models	2VO or BCCAO	Global chronic cerebral hypoperfusion via permanent occlusion of both CCAs (common carotid artery)	<ul style="list-style-type: none">○ Forebrain ischemia model○ WM rarefaction○ Axons and myelin damage○ Hippocampal (CA1) and cortical neuronal damage○ Striatal infarctions○ Increased inflammation○ BBB disruption (temporary–maximum at 3 days)○ Glial activation (mainly in WM)○ Oxidative stress	<ul style="list-style-type: none">○ Rapid drop in CBF○ Variable extent of ischemic lesions○ Vendor and strain based variabilities○ Damage to visual pathway/retinal perfusion○ Optic nerve and tract damage may influence cognitive tests○ Does not follow SVD pathophysiology, and affects microvascular flow via occlusion of both CCAs
	4VO	Consecutive occlusion of both vertebral arteries and both CCAs	<ul style="list-style-type: none">○ Neuronal damage (cortical, hippocampal)○ Early neurodegeneration in hippocampus○ Increased immunoreactivity	<ul style="list-style-type: none">○ Is a 2 step-2 day procedure○ Damage to visual pathway/retinal perfusion○ Variability in surgical procedure○ Variability in occlusion durations
	UCCAO	Chronic cerebral hypoperfusion via permanent occlusion of a single CCA	<ul style="list-style-type: none">○ WM rarefactions (delayed, corpus callosum)○ Decreased synaptic plasticity○ Increased inflammatory responses○ Neurodegeneration (mild)	<ul style="list-style-type: none">○ Vendor and strain based variabilities○ Infarcts may not be histologically detectable○ Spatial memory and learning are not affected○ Mild short term memory loss only
	BCAS(most promising VaD model)	Bilateral occlusion of CCAs using a micro-coil (recommended diameter 0.18 mm; but may vary from 0.16 mm–0.22 mm)	<ul style="list-style-type: none">○ WM lesions and rarefactions in Corpus callosum○ Increased inflammation○ BBB disruption○ Delayed hippocampal damage and atrophy○ Decreased brain metabolism○ Gliosis–microgliosis, astrogliosis	<ul style="list-style-type: none">○ Complete occlusion of both CCAs in mice increases mortality○ Delayed WM lesions in mice due to milder CBF reduction○ CBF variability between strains might affect BCAS effectiveness○ High mortality, CBF reduction and gray matter damage with 0.16 mm coil○ Damage to vessel endothelia○ Spatial memory is not affected○ Amyloid beta deposition has been reported○ Does not follow SVD pathophysiology, and affects microvascular flow via occlusion of both CCAs
Multiple infarcts and thromboembolism model (clinically most relevant model)		Injection of microemboli into the ICA (internal carotid artery) Emboli: cholesterol crystals/microspheres or microbeads/thrombi Size range: 40–100 μm	<ul style="list-style-type: none">○ Infarcts in cortex and striatum○ Microglial, macrophage and astroglial activation○ Increased inflammation○ Mitochondrial dysfunction○ Oxidative stress○ Hippocampal damage○ Impaired neuro-transmitter mechanisms○ BBB damage	<ul style="list-style-type: none">○ Short term or transient deficits○ Variability in emboli material, size, and numbers makes comparisons difficult
High fat diet model		Free feeding of High fat diet (western diet 40% fat, Lard based 60% fat)	<ul style="list-style-type: none">○ Hippocampal neuronal damage: impaired hippocampal synaptic plasticity and loss of dendritic spine density○ Increased inflammation○ Oxidative stress○ Decreased BDNF levels○ NF-κB activation○ Metabolic syndrome	<ul style="list-style-type: none">○ Variability in duration of HFD○ Variability in % of high fat and source of fat
Models using risk factors to induce VaD	Hypertension	Stroke prone spontaneously hypertensive rats (SHRSP)	<ul style="list-style-type: none">○ Cortical (~80%) and striatal infarcts○ Hippocampal WM and gray matter decrease○ Hippocampal astrogliosis○ WM damage with gliosis○ Inflammatory responses○ Endothelial injury (causing vessel wall damage and rupture, BBB disruption, microbleeds)○ Small vessel wall hardening○ Edematous injury	<ul style="list-style-type: none">○ Lesion volume and stroke outcome are variable○ Neurological deficits may influence cognitive testing if selection is not thorough○ Regular and careful assessment of animals for neurological stroke like symptoms, body parameters and weight throughout the study is required○ Visual pathway can be affected
	Diabetes	<ul style="list-style-type: none">○ T1DM, T2DM rat and mouse models	<ul style="list-style-type: none">○ BBB disruption○ Hippocampal damage (decreased synaptic plasticity, dendritic density, neurogenesis)○ Inflammatory responses○ Oxidative stress○ Hippocampal microglial activation	<ul style="list-style-type: none">○ Careful evaluation of whether VaD or AD has onset is required.

indicated a higher mortality with a 2 stage occlusion (2 CCAs followed by 2 VAs) in comparison to a 3 stage occlusion (2 VAs followed by one CCA then another CCA) (Neto et al., 2005). The 3 stage 4VO also induced

significant cognitive impairment tested by the aversive radial arm functional test (Neto et al., 2005). The pathophysiological changes associated with the 4VO model include ischemic neuronal damage

and low seizure incidence (Pulsinelli and Brierley, 1979) in middle aged rats, and hippocampal and cortical neuronal damage was observed and cognitive impairment was indicated by radial maze test (Ferreira et al., 2011; Dias Fiuza Ferreira et al., 2013), and poor spatial learning and memory indicated by water maze test (Kim et al., 2011). Early neurodegeneration in the hippocampus and cortex identified by Fluoro-Jade and GFAP (Glial fibrillary acidic protein) expression has been reported as early as 24 h after 4VO that increased progressively up to 72 h; along with progressively increased immunoreactivity identified by tau expression up to 72 h after 4VO (Cespedes et al., 2013).

There are several limitations to the 4VO model as well. Firstly, the surgery is performed in 2 steps and is at least a 2 day procedure. Secondly, methodological differences in the order of vessel occlusion exist. Thirdly, different occlusion periods of CCA ranging from 10 min to permanent occlusion have been reported in literature (Pulsinelli and Brierley, 1979; Neto et al., 2005). Functional outcome is dependent on the occlusion duration. Strain and vendor based discrepancies have also been noted in the 4VO model by the developers of this model (Pulsinelli and Buchan, 1988), maybe in part due to differences in collateral blood supply. These variabilities pose a big setback when comparing results of different studies.

Unilateral CCA occlusion (UCCAO) animal model

In this model, one of the CCAs is permanently ligated using a suture (Yoshizaki et al., 2008). Mice subjected to UCCAO suffered from chronic cerebral hypoperfusion, delayed WM damage in the corpus callosum (Yoshizaki et al., 2008), inflammatory responses such as elevated proinflammatory cytokines and decreased anti-inflammatory cytokines (Yoshizaki et al., 2008), decreased synaptic plasticity (Zhao et al., 2014) and mild neurodegeneration (Zhao et al., 2014). While, no significant loss was observed in learning and spatial memory; spontaneous alternation; and spontaneous motor activity in UCCAO mice, significantly increased anxiety (but not depression) and decreased exploration were observed from the open field and elevated plus maze tests, and short term memory impairment was observed using the novel object memory test (Yoshizaki et al., 2008; Zhao et al., 2014). A disadvantage of this model is that histological infarcts are not readily detectable.

Bilateral CCA stenosis (BCAS) model

The bilateral CCAs are consecutively occluded by placing micro-coils around the CCA with a 30 min interval between left and right CCA occlusions (Shibata et al., 2004). It is crucial to carefully select the inner core diameter of the micro-coil as this determines the extent of cerebral damage. WM lesions in the corpus callosum were observed starting at 3 to 7 days after BCAS in rats and after 14 days in mice (Shibata et al., 2004). This delay has been attributed to a milder CBF reduction in mice compared to rats. In mice, CBF reduction recovered from about 60–70% at 2 h after BCAS to greater than 80% by 1–3 months (Nishio et al., 2010). A decrease in brain metabolism (^{18}F -FDG uptake) has been reported with glucose uptake reduced in the cerebral cortex and striatum (at 2 h 70% and at 2 months 88% of pre-BCAS values) and hippocampus (6 months: 20% reduction) (Nishio et al., 2010). BCAS in mice also induces delayed hippocampal atrophy (Nishio et al., 2010), and induces inflammatory responses such as MMP activations, gliosis and BBB disruption (Nakaji et al., 2006). Cognitive dysfunction in mice was observed even at 5–6 months after BCAS with deficits in working and reference memory evaluated using radial arm and Barnes maze; and motor deficits observed till 3 months using a beam test and gait analysis; however no reference memory deficits were observed at 30 days after BCAS and spatial memory loss has not been reported (Nishio et al., 2010; Shibata et al., 2007). The cognitive dysfunction correlates to the observed WM damage observed starting at 14 days in mice and 3–7 days in rats which may be responsible for the loss in working memory and delayed hippocampal damage at 5–6 months may

cause the delayed loss in reference memory (Ihara and Tomimoto, 2011).

Variations in this model mainly center on the choice of coil diameter which may influence mortality and degree of brain damage. In mice, the use of 0.16 mm coil escalated the mortality rates to about 75% versus approximately 10–20%, when using coils of core 0.22 mm, 0.20 mm, and 0.18 mm, respectively (Shibata et al., 2004). This might be due to the greater CBF reduction with decreasing coil diameter. In mice, the 0.18 mm micro-coil has been recommended with a promise of high reproducibility (Shibata et al., 2004). While in rats damage to the visual pathway may occur and interfere with cognitive evaluation (Yamamoto et al., 2006), when using mice, little to no damage was observed in the gray matter and visual pathway due to a milder CBF decrease and some residual blood flow within the CCAs and its branches (Shibata et al., 2004). Lastly, the coils have to be procured from a company (like Sawane Spring Co., Ltd., Hamamatsu, Japan) and are typically not reusable which could compound costs when using large animal numbers. Additionally, accumulation of amyloid beta which is typical in AD had been reported after BCAS in mice (Khan et al., 2015). The BCAS model does not reflect SVD pathology, instead the occlusion of both CCAs induces chronic hypoperfusion and affects microvascular flow to induce VaD (Khan et al., 2015).

Multiple infarct and thromboembolism models

In a study involving 425 subjects subjected to dementia evaluation and brain autopsy post death, cortical and sub cortical microinfarcts were found in about 30% of subjects (Arvanitakis et al., 2011). Microinfarcts increased the probability of dementia, in particular, multiple cortical microinfarcts were a significant risk factor. Microinfarcts were associated with cognitive decline particularly perceptual speed, semantic and episodic memory (Arvanitakis et al., 2011). Therefore, the multiple infarction VaD model may be a clinically relevant model. Multiple infarction animal models can be induced by thromboemboli, cholesterol crystals, microbeads or micro-spheres.

Thromboembolic multiple infarction VaD model

Cerebral emboli and its association with the progression of VaD and AD were recently studied in humans (Purandare et al., 2012). 60 VaD patients were observed for spontaneous cerebral emboli entering the middle cerebral artery (MCA) and decline in cognitive abilities over a period of 2 years using trans-cranial Doppler ultrasound every 6 months. In 45% VaD patients, spontaneous cerebral emboli were positively identified and associated with greater cognitive decline. Studies have shown that a thromboembolic model in rats can cause significant hippocampal injury and cognitive impairment (Zhang et al., 2013) with the size of emboli playing a critical role in determining the extent of neurological deficits and hippocampal injury (Zhang et al., 2013). When emboli of diameter 48–74 μm was employed, at 60 days post embolization significant hippocampal damage in the CA1, 2, 3 regions and poor performance in the water maze test were observed (Zhang et al., 2013).

Micro-spheres induced multiple infarction VaD model

Multiple infarcts can be induced in the rat brain's cortex, striatum and hippocampus, by injecting about 700–900 micro-spheres of 48–50 μm diameter into the right internal carotid artery (ICA) (Takagi and Takeo, 2003; Miyake et al., 1993). Sustained decrease in CBF, neuronal damage and impaired energy and neurotransmitter metabolisms were observed in the ischemic side of the brain. These ischemic damages resulted in cognitive impairment. Long escape latency was observed in the water maze test about a week after intravascular embolization, suggesting spatial learning impairment and poor performance in the active and passive avoidance (Fukatsu et al., 2002; Takagi et al., 1997). Cerebral embolization as a model for VaD has been advocated also due to its induction of learning impairments in 3 tasks including

one trial active and passive avoidance task as well as two-way active avoidance response in a shuttle box, and the water filled multiple T-maze task (Kiyota et al., 1986). However, the deficits lasted only a few weeks and were not long term cognitive deficits.

Cholesterol crystals induced multiple infarction VaD model

Another model used cholesterol crystals sized 60–100 μm injected into the ICA to induce multiple microinfarcts in the brain, and induces cognitive loss (Rapp et al., 2008a). Both young adult and middle-aged rats were subjected to either a single injection or repeated, bilateral injections given 2 weeks apart. Cognitive testing included open field, motor learning, and Barnes Maze tests. Activation of matrix metalloproteinase (MMPs), microglia and astrocytes indicative of inflammation was observed mainly in the striatum and hippocampus (Rapp et al., 2008a). Middle aged rats after bilateral multiple injections showed cognitive dysfunction but not after single injections (Rapp et al., 2008a). Microembolization using cholesterol crystals can hence induce inflammation and minimal neuronal injury leading to cognitive dysfunction in older animals.

A similar microinfarct model using cholesterol crystals has been studied in mice (Wang et al., 2012). A single injection of 40–70 μm cholesterol crystals into the ICA produced multiple microinfarcts in the deep cortex, subcortical tissue, and hippocampus. These microinfarcts were associated with microglial and macrophage activation in its core as well reactive astrogliosis in its surrounding. Neuronal injury and death was progressive and increased with time over a period of 28 days after stroke (Wang et al., 2012). Delayed demyelination starting at 28 days and long lasting gliosis were present. Cognitive decline was measured using the novel object recognition test and hippocampal learning impairment was evident from contextual and tonal fear conditioning tests. The cognitive deficits observed at 7 and 14 days post microinfarct were not observed at 28 days (Wang et al., 2012).

Comparison of three multiple infarction VaD models

Rapp et al. also compared infarcts caused by embolism with microthrombi and cholesterol crystals (Rapp et al., 2008b). While thrombus fragments induced discrete infarcts of about 0.1–1.7 mm diameter, cholesterol crystals induced smaller infarcts specifically in the subcortical tissue. With thrombus fragments, the sites of astrocytic and microglial activation overlapped infarcts; using cholesterol crystals, BBB damage and microglial activation were widespread in the brain. These data clearly point out that the extent of brain damage, type of infarcts and associated inflammatory responses depend on the type and size of emboli used. To verify the association of microinfarcts with cognitive decline, a study employed controlled optical methods namely the 2 photon microscopy and occluded individual penetrating vessels on the cortical surface in the rat brain (Shih et al., 2013). They found that the occlusion of even a single penetrating vessel can lead to microinfarcts and cognitive impairment. In addition, multiple vessel occlusions resulted in coalesced cortical tissue damage, i.e. microinfarcts combining to become large cysts, despite the presence of unobstructed intervening penetrating vessels. This is an important finding of clinical relevance, that not only do microinfarcts lead to cognitive decline but multiple microinfarcts can coalesce and potentially have increased or additive adverse effects (Shih et al., 2013).

High fat diet induced VaD models

There is ample evidence suggesting a strong link between high fat diet (HFD) and cognitive deficits in hippocampus based tasks especially associated with the older population. However, the mechanisms and implications are yet to be fully understood. Rats fed a HFD for 3 months performed poorly in learning and memory tasks, and the extent of cognitive loss was found to be comparable to standard chow fed rats that were aged or had suffered brain damage (Winocur and Greenwood, 2005). The Rotterdam study (Kalmijn et al., 1997) that

investigates occurrences and contributing factors of various neurological diseases among elderly persons had reported that a HFD was associated with cardiovascular risks and dementia. They indicated that in people aged >55 years, intake of high total fat, saturated fat and cholesterol was related to high risks of dementia particularly vascular dementia. A study that fed rats a diet high in saturated fat and sugar reported cognitive deficits in hippocampal-dependent learning and memory processes and also indicated that loss of cognition may precede obesity (Davidson et al., 2013). However, another report from the Rotterdam study raised a question on the association of HFD with dementia risk (Engelhart et al., 2002) and concluded that a diet consisting of high fat (total, saturated, trans fat, cholesterol) was not associated with an increased risk of dementia or its subtype. Some studies have indicated that cognitive impairment and HFD induced oxidative damage were found only when 60% lard based HFD was used, but not with a typical Western diet of 40% HFD (Pistell et al., 2010; Morrison et al., 2010).

Models using risk factors to induce VaD

Spontaneously hypertensive rats stroke prone (SHRSP)

Hypertension and its association with stroke and dementia have been discussed under risk factors. SHR and SHRSP are the most popular rat strain used in hypertension investigation. While SHRSP rats and their control Wistar–Kyoto (WKY) rats have similar blood supply patterns to the brain, SHRSP rats (normotensive at birth) develop high arterial BP as they age (from 4 weeks to 30 weeks) to about 220 mm HG (by 12 weeks) and spontaneously develop ischemic lesions primarily in the cortex (~80%) and secondarily in the basal ganglia (Yamori et al., 1976).

When compared to WKY rats, SHRSP rats had poor learning and memory during their pre stroke phase with worse outcomes post stroke (Yamaguchi et al., 1994). SHRSP rats after stroke or when subjected to vessel occlusion models (such as UCCAO), with or without salt supplement demonstrate cognitive impairment and develop WM rarefaction and myelin damage, WM lesions with reactive gliosis, small vessel wall hardening, BBB disruption and inflammatory responses were observed (Jalal et al., 2012; Fredriksson et al., 1985; Chiba et al., 2012; Henning et al., 2010). Endothelial injury has been implicated to cause blood vessel damage and rupture leading to BBB disruption and microbleeds (Schreiber et al., 2013; Li et al., 2014a). In the hippocampus of SHRSP rats, by 4 months a decrease in white matter and by 6 months a decrease in gray matter in the CA1 and dentate gyrus along with astrogliosis in the CA1 region was observed (Sabbatini et al., 2002). In addition to the SHRSP, a model using middle aged SHR rats has been suggested as an early cerebral SVD model (Kaiser et al., 2014); however further studies are required to understand if a similar pathology such as SHRSP ensues in SHR rats.

One important variation when using SHRSP rats is that they routinely suffer from stroke-like neurological deficits which range from mild to severe paralysis or even death depending on the size of ischemic lesion. Careful selection of animals factoring in motor deficits/paralysis is needed. Also, neurological deficits and body weight have to be evaluated throughout the study on a regular basis. Visual lesions have been detected by MRI in aged female SHRSP rats and animals show mild incoordination (Henning et al., 2010). Typically, when using models with multiple co-existing or cause-effect conditions (here, hypertension and stroke), analyzing individual effects is difficult and the effects of treatment for one may interfere with results of other. It is relevant to evaluate the effects of hypertension treatment on dementia, and several efforts in this regard have been discussed earlier in the risk factors-hypertension section of this article.

Diabetic mouse models

Both type one diabetes mellitus and two diabetes mellitus (T1DM, T2DM) as risk factors for VaD have been discussed earlier in this article. Briefly, a high dose or multiple low doses of streptozotocin are used for

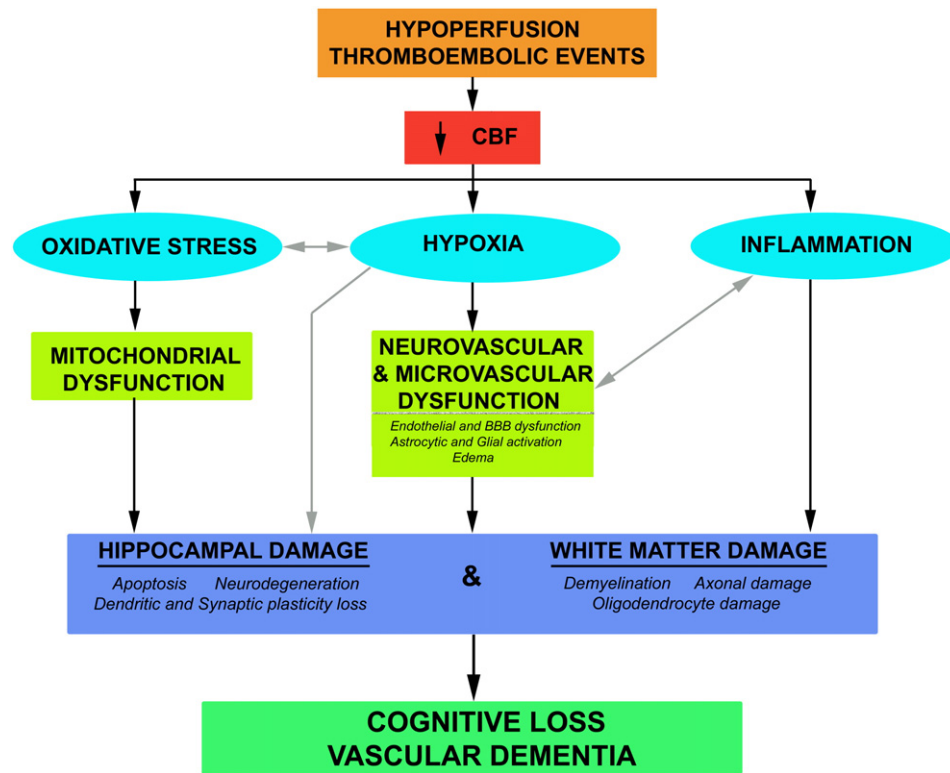


Fig. 3. Summarizes the various mechanisms implicated in the pathogenesis of VaD.

T1DM induction and several obese (readily available, HFD induced) and some non-obese mice and rats (GK rats, etc) are used to model T2DM (King, 2012). In STZ induced diabetes, long term cognition has been shown to be affected by diabetes induced alterations to the microvasculature and BBB disruption (Huber et al., 2006). In the hippocampus, genes associated with neurogenesis and synaptic plasticity were found to be decreased in T1DM mice (Thomas et al., 2014). Additionally the inflammatory TL4 (toll-like receptor 4) signaling pathway and oxidative stress have been implicated in T1DM cognitive decline such as poor learning, memory and anxiety (Kawamoto et al., 2014; Alvarez et al., 2009). Upon recurrent or moderate hypoglycemia in T1DM rats, hippocampal microglial activation, decreased dendritic density and oxidative stress have been associated with cognitive deficits evaluated with Barnes maze and open field tests (Won et al., 2012). In T2DM induction, HFD is often employed, and the effects of HFD on cognition have been discussed earlier in this article. Cognitive loss has also been reported in other T2DM models as well and associated with BBB dysfunction, inflammatory responses and affected neuronal plasticity and neurovascular coupling (Tsukuda et al., 2007; Serlin et al., 2011).

In diabetic animal models while cognitive dysfunction has been well established, it should be noted that both VaD and AD or even mixed dementia like symptoms have been reported and careful assessment of amyloid beta pathology, vascular and white matter changes as well as cognitive evaluations are required when choosing animal models to study VaD (Wang et al., 2014; Li et al., 2015). Studies on the beneficial effects of diabetes treatments on VaD are warranted.

Age

Age is a major risk factor for dementia. Age related cognitive decline that worsens with increasing age has been reported by several studies in both mice and rats (Goldman et al., 1992; Park et al., 2007). It may be important to factor in age, and study aged animals in VaD animal models. However, some of the difficulties involved in studying aged animals include mortality, severe neurological deficits after stroke, occurrence of tumors, and the resulting requirement of using increased

animal number to be conclusive of results (Manwani et al., 2014; Lindner et al., 2003; Bruley-Rosset et al., 1981).

Pathophysiology and molecular mechanisms of VaD

It is important to understand the pathophysiology of the disease before establishing a good animal model to test treatments. The pathology and mechanisms underlying VaD are yet to be fully understood. It must be noted that the clinical signs and symptoms of VaD may vary depending on the cause and type of VaD and site and size of infarction/damage. Hence, a consensus on defined symptoms and diagnostic procedure has not yet been reached, and routinely neuropsychological and behavioral profiles along with cognitive testing are carried out.

In VaD, chronic hypoperfusion and thromboembolic events, lead to a decrease in CBF, hypoxia, oxidative stress and trigger inflammatory responses. The periventricular WM, basal ganglia, and hippocampus are highly susceptible to hypoperfusion induced lesions. Disruption of the prefrontal–basal ganglia circuitry induces cognitive deficits which is typical in VaD (summarized in Fig. 3).

Hypoxia induced oxidative stress leads to mitochondrial dysfunction (and vice versa), neuronal damage and apoptosis via nitric oxide synthase (NOS) pathway, malondialdehyde content, release of reactive oxygen species and free radicals (Li et al., 2013; Ma et al., 2013; Zhang et al., 2014b; Huang et al., 2007; Ritz et al., 2012). Oxidative stress imbalances the ratio of antioxidants and reactive oxygen species resulting in damage to vessel endothelia, glial and neuronal cells, resulting in neurovascular uncoupling and further CBF reduction (Liu and Zhang, 2012). The excess reactive oxygen species can disrupt mitochondrial function and further induce hypoxia and oxidative stress (Zhang et al., 2014b). Cerebral hypoxia can lead to cell death and microvascular dysfunction marked with an increase in vascular inflammatory factors as well as trigger endothelial dysfunction, vascular and BBB leakage, and increases neuro-inflammatory response (Gill et al., 2010).

Inflammatory factors such as Matrix Metalloproteinases (MMPs) and microvascular dysfunction degrade the BBB (Candelario-Jalil et al.,

2011; Reuter et al., 2015) and increase BBB permeability to infiltration of inflammatory factors like interleukins (IL-1, IL-6), MMPs (MMP 2,9), TNF α (tumor necrosis factor), TLR4 (toll-like receptor 4), and C-reactive protein (Iemolo et al., 2009) (Li and Lai, 2007). Upon entry into the brain, these inflammatory factors exacerbate WM damage (demyelination, axonal loss, oligodendrocyte degeneration), cause neuro-degeneration and cell death as well as enhance neuroglial inflammation (Chen et al., 2011). Glial secretion of inflammatory factors can exacerbate WM lesions and demyelination by damaging oligodendrocytes (Wang et al., 2010). Cerebral WM is highly susceptible to hypoxia induced damage owing to its limited blood supply and poor collateral blood flow in deep structures (Back et al., 2002). In VaD, WM damage arises primarily from demyelination that is attributed to hypoxia induced oligodendrocyte damage (Ihara et al., 2010). Oligodendrocyte shrinkage and death as well as damage to oligodendrocyte progenitor cells reduce or hinder remyelination (Ihara et al., 2010). Demyelination delays neural signal transmission and leads to cognitive loss. The result of the inflammatory cascade in the hippocampus is the impairment of neurogenesis, neuronal progenitor cell proliferation, synaptic plasticity and dendritic spine density (Park et al., 2010) (Stranahan et al., 2008). Hippocampus based learning and memory deficits ensue.

The vicious cycle of oxidative stress, endothelial and microvascular dysfunction and inflammation exacerbate cerebral damage. The neurovascular unit, a conceptual model that describes functional interactions and signaling between neurons, capillaries, and glia in the brain (Chen et al., 2014a) is dysregulated largely by the interplay between oxidative stress and inflammation resulting in increased BBB disruption, edema, neurovascular uncoupling, and neuronal damage. There exists a complex molecular interaction between these mechanisms and together they result in the disruption of brain homeostasis and neurovascular unit uncoupling (Stanimirovic and Friedman, 2012). Endothelial injury and platelet activation result in microvascular damage by either adhesion and vasoconstriction or thrombosis and vascular occlusion (Shih et al., 2013; Barker et al., 2014; Song et al., 2014). Such damage to the arteries and arterioles that supply the deep WM of brain results in white matter infarctions (Brun, 1994).

A rare VaD subtype called CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a genetic mutation in the Notch3 gene. Among the genes, apolipoprotein E (apoE) has received special attention. While in AD, carriers of the apoE4 allele account for almost 65–80% of all AD patients and its role as a major risk factor has been well documented, there are several conflicting reports about its role in VaD (Rohn, 2014). The presence of cleaved apoE in the hippocampus of VaD brain has been reported recently (Rohn et al., 2014). It has been suggested that the harboring of one or both apoE4 alleles might be a VaD risk factor but not as potent as it is for AD (Rohn, 2014).

While the VaD disease pathology has been studied to a certain extent and various factors leading to cognitive dysfunction identified, there is still wide scope in understanding the pathology and broader picture of disease mechanism. There is also a need to develop markers to clearly differentiate VaD from other forms of dementia like AD.

Treatment options

At present, there is no FDA approved treatment for VaD. Hence, several drugs used for AD or that are known to lower cardiovascular risk factors are being employed or studied. These yield modest benefits and control cognitive impairment associated with mild to moderate VaD. The current treatment strategies are mainly attempting to control the progressive nature of VaD induced cognitive dysfunction. The following is a brief discussion of some of the drugs employed in VaD treatment.

Statins are cholesterol lowering drugs. While Simvastatin (oral, 5 mg/Kg for 4 weeks) was found to improve cognition, reduce

depression, decrease blood serum triglycerides to normal values and increase the number of pyramidal neurons in HFD fed rats (Can et al., 2012), the ROCAS (Regression of Cerebral Artery Stenosis) clinical trial (Mok et al., 2009) concluded that Simvastatin (20 mg/day, daily for 2 years) might at best delay the progression of cerebral WM lesions in patients who already have severe WM lesions.

The *N-methyl-D-aspartate* (NMDA) receptor is the predominant molecular device for controlling synaptic plasticity and memory function (Lai et al., 2014). Memantine is an NMDA antagonist and is FDA approved for the treatment of AD. In mild to moderate severity VaD patients Memantine (10 mg/day, twice a day for 28 weeks) treatment improved cognition (Orgogozo et al., 2002). However, NMDA receptor antagonists are also known to cause cognitive loss and induce hallucinations (Lipton, 2004).

Donepezil, an oral drug which acts centrally to reversibly inhibit acetylcholinesterase appears to yield some benefits in AD and VaD. Two large clinical trials have reported that Donepezil (5 or 10 mg/day, up to 54 weeks) can easily cross the BBB, is well tolerated in humans and improves cognitive functioning (Wilkinson et al., 2003; Wilkinson et al., 2010). However, it may cause gastrointestinal side effects (Dunn et al., 2000) and has to be used with caution.

Cell-based therapy, such as transplantation of EPCs (endothelial progenitor cells), BMSCs (bone marrow stromal cells) or HUCBCs (human umbilical cord blood cells) induces secretion of trophic factors, increases angiogenesis, neurogenesis and white matter remodeling after stroke (Liu et al., 2014a; Liu et al., 2014b; Yan et al., 2014; Chen et al., 2014b; Cui et al., 2012); and may also hold promise in attenuating cognitive dysfunction. HUCBC treatment improves cognition and reduces amyloid- β -associated neuropathology in Alzheimer mice (Darlington et al., 2013) and also improves spatial memory in neonatal hypoxia-ischemia (de Paula et al., 2012). In addition, MSCs modulate longitudinal changes in cortical thickness and reduce cognitive decline in patients with multiple system atrophy (Sunwoo et al., 2014).

Other therapies: Resveratrol treatment targets dementia by reducing oxidative stress (Ma et al., 2013), and improves cognition possibly through its anti-inflammation and anti-apoptotic actions (Li et al., 2014b). Other treatment strategies for neurodegenerative disorders as well as VaD include, TNF-alpha inhibition that significantly reverses hippocampus-dependent cognitive deficits by attenuating the inflammatory factors expression (Belarbi et al., 2012; Tweedie et al., 2007), and treatments targeting adult neurogenesis (Ruan et al., 2014). Pharmacological strategies that affect the dialog between the brain and peripheral immune system show promise as potential novel treatments for stroke (An et al., 2014) and may also benefit VaD.

Conclusions

This review has focused on VaD, its characteristics, risk factors, currently employed animal models as well as current treatment strategies. The limitations of this review article include, that stroke induced VaD has not been discussed. The clinical VaD testing criteria has only been briefly mentioned, as this has been dwelt upon by others, as indicated. The animal models discussed are limited to rodent models of vascular dementia. Using small animals (mice and rats) has several advantages: cost effectiveness, they can be observed for long periods of time, reproducibility and limited variability between testing groups, ease of behavioral and cognitive testing with readily available testing equipment and analysis software, the availability of transgenic mice enables evaluation of specific mechanisms and pathways, and testing therapeutic targets is cost effective as smaller doses are required due to smaller body mass of animals.

In the future, there is a need to adapt a standard set of cognitive evaluation criteria including types and time points of testing, and evaluation must encompass tests to assess learning and memory as well as behavioral deficits, motor deficits, anxiety and depression. Also, cognitive evaluation must not rely on the results of a single

learning and memory test; instead cognitive evaluation should incorporate several test results, and assess multiple aspects of cognition to be conclusive of VaD and rule out interference from optic pathways damage or neurological deficits. Such uniformity will enable comparisons of different rodent models to determine the most suitable model for evaluating treatment strategies. Understanding the underlying pathology and mechanism of disease is crucial for developing successful treatments of VaD. It is now possible with the aid of immunohistochemistry as well as imaging techniques to evaluate hippocampal atrophy, ischemic lesions, white matter damage, axonal and synaptic deficits, blood brain barrier integrity, inflammatory responses as well cerebral blood flow and perfusion among other mechanisms. The time course and interplay of these mechanisms in VaD should be clarified in order to develop successful interventions and treatments. While neuro-imaging is an important tool used for clinical diagnosis of dementias, experimental animal models have yet to fully exploit the use of MRI in understanding VaD. The role of microRNAs in VaD and their potential use as biomarkers or as treatment strategies has yet to be well explored, and future studies are warranted.

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