



Metabolic Syndrome and Vascular-Associated Cognitive Impairment: a Focus on Preclinical Investigations

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Abstract

Purpose of Review Metabolic syndrome is associated with an increased risk of vascular cognitive impairment or, in the more extreme, vascular dementia. Animal models are used to investigate the relationship between pathology and behaviour. This review summarizes the latest understanding of the role of the hippocampus and prefrontal cortex in vascular cognitive impairment, the influence of inflammation in this association while also commenting on some of the latest interventions proposed.

Recent Findings Models of vascular cognitive impairment and vascular dementia, whether they develop from an infarct or non-infarct base, demonstrate increased neuroinflammation, reduced neuronal function and deficits in prefrontal and hippocampal-associated cognitive domains. Promising new research shows agents and environmental interventions that inhibit central oxidative stress and inflammation can reverse both pathology and cognitive dysfunction.

Summary While preclinical studies suggest that reversal of deficits in vascular cognitive impairment models is possible, replication in patients still needs to be demonstrated.

Keywords Vascular cognitive impairment · Vascular dementia · Cognition · Hippocampus · Prefrontal cortex · Preclinical models

Abbreviations

2-VO	Two-vessel carotid artery occlusion
CCAO	Occlusion of the common carotid arteries
ILs	Interleukins
MCAO	Middle cerebral artery occlusion
MetSyn	Metabolic syndrome
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
Nrf2	NF-E2 p45-related factor 2
siRNA	Small interfering RNA
SHR/SP	Stroke-prone spontaneously hypertensive rat
STZ	Streptozotocin
tCDS	Transcranial direct current stimulation
TLR-4	Toll-like receptor 4
TNF	Tumour necrosis factor
TXNIP	Thioredoxin-interacting protein

VCI	Vascular cognitive impairment
VD	Vascular dementia

Introduction

Metabolic syndrome (MetSyn) is a cluster of metabolic disturbances—abdominal obesity, hypertension, glucose intolerance and atherogenic dyslipidemia (increased plasma triglycerides and decreased high-density lipoprotein cholesterol concentration)—which is associated with increased risk for heart disease, type 2 diabetes (T2D) and stroke [1, 2]. Current evidence suggests that 20–45% of the population worldwide suffer from MetSyn [3] and while the prevalence is highest among people aged over 60 [4], recent studies show that its incidence is increasing in younger age groups [5] and across all populations [6–8].

The association between MetSyn and cardiovascular risk is well studied; however, the identification of how MetSyn metabolic changes can lead to functionally debilitating changes in cognition is less understood. Vascular cognitive impairment (VCI) is a form of cognitive deficit caused by vascular abnormalities [9]. The most severe form is vascular dementia (VD), which refers to a subgroup of patients who have dementia that is largely attributable to cerebrovascular

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pathology, often estimated to be ~15–30% of dementia cases [10]. Studies demonstrate that patients with VCI display deficits in multiple cognitive domains including memory, executive functioning, processing speed and overall intellectual functioning [11–13] which can be captured under the terminology of higher order function. Anhedonia, apathy, anxiety and depression are also frequently observed in patients with VCI [14, 15].

There are currently no medications that successfully treat VCI. Interventions such as antihypertensives and statins focus on managing risk factors [16] while both these classes of medications as well as the medications used to treat Alzheimer's disease have little to no effect on reducing or slowing cognitive deficits [17]. Given the lack of effective pharmaceuticals, progress in our understanding of the pathophysiological mechanisms involved in VCI and VD is crucial for the development of new strategies around protection and treatment.

Pathological analysis of brain changes in VCI and VD includes both neuroimaging and pathology-confirmed diagnosis [9]. Cerebrovascular changes such as lesions, microinfarcts and arteriolosclerosis are observed along with white matter hyperintensities representing white matter degeneration [18, 19]. At a cellular level, we recognize that atypical neuroinflammation and cell death are observed with levels of inflammatory markers altered in both plasma and cerebrospinal fluid [20]. Inflammatory mechanisms disrupt cerebrovascular integrity via glial activation and increased pro-inflammatory interleukins (ILs) and tumour necrosis factor (TNF)- α production, inducing vascular tissue injury and neurodegeneration [21], and centrally endothelial and neuronal cell damage [21].

The hippocampus and prefrontal cortex play an essential role in cognitive functioning. The hippocampus is important in spatial memory and episodic memory, information formation and processing and associated behavioural regulation [22], while the prefrontal cortex plays a central role in

executive functioning including attention, planning, decision-making, perception and processing [23]. Patients with VD show hippocampal atrophy [24] which is attributed to loss of neurons [25] and reduction in cerebral microvasculature [26]. Post-mortem studies show IL-1 β [27] and TNF- α expression [28] in the hippocampus in VD patients is significantly higher than in age-matched controls demonstrating an influence of inflammation. However, in the prefrontal cortex in VCI and VD, white matter degeneration [29] linked to neuronal dysfunction and degeneration [30] has been shown, but there are few reports of changes in inflammatory markers in this region. It is unclear if no changes have been found or if the target of the hippocampus as the 'memory centre' as the prime region of investigation has reduced investigation into other brain regions.

From our understanding of cognition and cognitive deficits in its many forms, it is clear that a 'one area fits all' concept cannot address why cognitive deficits occur after metabolic syndrome and its associated diseases. The use of preclinical models with controlled parameters is advantageous to mimic certain aspects of MetSyn and VCI in animals and explore the relationship between brain pathology and the cognitive deficits associated with the disorders.

Models of Vascular Cognitive Impairment

VCI animal models are largely based on modelling the cerebrovascular pathology observed in patients [31] (Table 1). Transient or permanent middle cerebral artery occlusion (MCAO) or occlusion of the common carotid arteries (CCAO) are routinely used as models of stroke and VCI to induce cerebral hypoperfusion, infarction, hypoxia and hypoperfusion of white matter due to inadequate blood supply [32–34]. This is accompanied by damaged white matter with a proliferation of astrocytes and activated microglia, disintegration of white matter tracts and a reduction in

Table 1 Summary table of most used VCI preclinical models

Preclinical models	Performed by	Pathology	References
Middle cerebral artery occlusion (MCAO)	Transient or permanent middle cerebral artery occlusion	Hypoperfusion, infarction, cerebral ischemia, neuronal lesions, damaged white matter tracts	[19, 32]
Occlusion of the common carotid arteries (CCAO)	Transient or permanent bilateral common carotid artery occlusion	Hypoperfusion, infarction, cerebral ischemia, neuronal lesions, damaged white matter tracts	[87]
Stroke-prone spontaneously hypertensive rat (SHR/SP)	Established from a sub-strain of spontaneously hypertensive rats	Hypertension with progressive blood pressure increase during young adulthood, wall thickening in small arteries Microvascular dysfunction, blood–brain barrier breakdown, cerebrovascular lesions, hypoxia, hypoperfusion, white matter damage	[36, 37, 88]

myelin [35]. Alternatively, the stroke-prone spontaneously hypertensive rat (SHR/SP) is a non-surgical VCI model. This model exhibits brain lesions predominantly within the cerebral cortex and chronic vessel changes [36, 37] leading to cortical degeneration [38].

Metabolic disturbance can be used to model systemic cause or as an adjunct to the aforementioned models with a number of rodent models that encompass features of MetSyn. Some models are inbred strains selected for one or more traits underlying MetSyn—most commonly the SHR (spontaneous hypertensive rat) modelling hypertension. Others are population models with genetic risk for MetSyn traits, such as Zucker rats which model obesity and *db/db* mice which are a model of T2D. A third group are MetSyn traits induced by environmental stressors such as being fed high-fat and/or sugar diet [39] or administration of *streptozotocin* (STZ), a widely used chemical for the induction of experimental diabetes in rodents [40].

With regard to neuroinflammation, both infarct and non-infarct models of VCI demonstrate upregulation of inflammatory cells and markers. Astrocytes and microglia are activated in the brain [41] and pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α are increased [42, 43]. Inflammatory mediators such as matrix metalloproteinases are also upregulated [44].

Cognitive tests in VCI models demonstrate impaired memory. Spatial reference memory and working memory is deficient in VCI models [45, 46] which is influenced largely by the hippocampus. In this review, we will focus on the latest findings concerning hippocampal and prefrontal cortex pathology and cognitive deficits in VCI models, and endeavour to assess the plethora of new generation treatments proposed to reverse these.

Hippocampal and Prefrontal Pathology in VCI Models

Carotid artery occlusion and MCAO models produce a loss of hippocampal neurons [47], impaired spatial memory [48–50], elevated hippocampal levels of TNF- α and IL-6, as well as increased apoptotic cell death in the hippocampus [50]. Much less is known about changes in prefrontal cortices in preclinical VCI and VD models; however, a recent study has demonstrated that two-vessel carotid artery occlusion (2-VO) reduced learning in a novel object recognition prefrontal-dependant test and lowered expression of synaptic markers in the prefrontal cortex [51•].

Utilizing a STZ/MCAO MetSyn-VCI model, researchers observed that diabetes induced hippocampal-dependant impaired cognitive function in the Y-maze, social recognition and novel object recognition tasks in concert with upregulation of NLRP3 (NOD-, LRR- and pyrin

domain-containing protein 3) inflammasome expression in the hippocampus [52•]. These effects are further increased by MCAO stroke. This hippocampal inflammatory response is accompanied by higher levels of hippocampal cell death, vascular remodelling and greater astrocyte reactivity [52•]. Increased NLRP3 has also been observed in the hippocampus of the CCAO model of VCI [53], along with shrinkage, disorganization and loss of hippocampal neurons [54] and an impairment in spatial memory as observed by the Morris water maze task [54, 55] and radial arm maze [56]. Protein and mRNA levels of toll-like receptor 4 (TLR4) were increased after CCAO in microglia and neurons of the hippocampus [57] and the downstream inflammatory cytokines (IL-6) and TNF- α [57] while microvessels were observed to be shorter and fragmented [56].

Looking at non-surgical models, a decrease in neuron number and vitality is observed in the frontal cortex and hippocampus of Zucker rats, along with a reduction in synaptic markers and a memory retention deficit in the passive avoidance task [58, 59]. Conversely in the *db/db* model hippocampal long-term potentiation is inhibited and memory impaired [60, 61] while (like surgical VCI models) inflammation and neuronal pathology is increased in the hippocampus and prefrontal cortex [61, 62]. High-fat diet-induced obesity also causes cognition impairment, downregulation of neuroplasticity-associated proteins and increases in inflammation including astrocytic reactivity in the hippocampus and prefrontal cortex [63–65].

Based on these recent studies models of VCI and VD, whether they develop from a surgical or metabolic base, deficits in prefrontal and hippocampal-associated cognitive domains, decreased neuronal function and increased neuroinflammation are observed. However, we are little closer to identifying the cellular and molecular mechanisms underlying VCI and VD. Working backwards from interventions that show attenuation of deficits is providing a potential alternative path to identifying potential targets for treatment of VCI and VD.

New Generation Treatments and Environmental Interventions

Several new treatments have been proposed to reverse the cognitive and pathological deficits in animal models of VCI. These include anti-inflammatory, antihypertensive or antioxidant pharmacological interventions that may guide researchers towards appropriate mechanisms of action for human treatments. Other potential interventions are environmental, where the mechanisms are often poorly understood.

Injection of MCC950, a selective inhibitor of the NLRP3 inflammasome, after reperfusion in the STZ/MCAO MetSyn-VCI model ameliorated the diabetes-mediated deficits

in hippocampal-dependant memory, lowered cell death of the neurons in the CA1 and dentate gyrus regions of the hippocampus and reduced levels of IL-1 β and NLRP3 after MCAO [52•], suggesting that NLRP3 is a potential therapeutic target to treat cognitive impairment. In another study, osthole, a coumarin Chinese herb compound and inhibitor of NLRP3 protein expression, attenuated cognitive dysfunction in a VCI rat model induced by CCAO, evidenced by reversing spatial and working deficits, and inhibiting microglia activation in the hippocampus [66]. This notion is further strengthened by a recent study from Du and colleagues where acupuncture treatment reduced cognitive decline and hippocampal neuronal death in a model of VCI induced by CCAO by decreasing NLRP3 inflammasome and IL-1 β expression in the hippocampus [53]. The molecular mechanisms of acupuncture treatment in this model are suggested to be via inhibition of thioredoxin-interacting protein (TXNIP) which plays a vital role in NLRP3 inflammasome activation, with TXNIP small interfering RNA (siRNA) producing similar effects as acupuncture on memory and hippocampal neuron survival in the CCAO VCI model [53, 67]. In a further 2-VO study, acupuncture treatment reduced the levels of inflammatory cytokines in the hippocampus which was associated with lowered expression of TLR4 in the microglia, but not neurons, of the hippocampus [57]. A TLR4 antagonist, TAK-242, had similar effects as acupuncture on inflammation in these rats, while the TLR4 agonist lipopolysaccharide inhibited the beneficial effects of acupuncture [57]. In patients, inflammasome activation and cytokine production is related to the risk factors of VCI. A 2022 article by Poh and colleagues summarize these effects [68•] and report that therapeutic agents targeting IL-1 β and IL-18 are currently undergoing investigation in clinical trials and showing positive results in patient outcomes [68•, 69].

Chronic 3-month treatment with the antihypertensive amlodipine, a voltage-dependent Ca²⁺-channel blocker in BPH/2 mice prevented hypertension-related damage to functional hyperemia through the diminished activity of the capillary endothelial cell inward-rectifier potassium channel, Kir2.1 [70]. Interestingly, this result was not reproduced with the antihypertensive losartan, an angiotensin II receptor antagonist [70], aligning with clinical findings which demonstrate that calcium-channel blockers provide greater cerebrovascular protection than angiotensin-related antihypertensives in the prevention of dementia [71].

Recent studies suggested that antioxidants also have promising effects in VCI and VD models. The Chinese herb mix Chitosan reduces hippocampal-memory impairment and reduces neuron cell loss induced by CCAO while also significantly reversing reactive oxygen species production, neuronal apoptosis and microglia overactivation in the hippocampus through activation of the antioxidative response element Nrf2 (NF-E2 p45-related factor 2) causing the

subsequent upregulation in the expression of many cytoprotective enzymes [72]. Meanwhile, Pinocembrin, a flavonoid with antioxidant properties [73] alleviated learning and memory deficits induced by CCAO and attenuated hippocampal neuronal damage by inducing the upregulation of the Reelin-Dab1 signalling pathway in the hippocampus [74], previously reported to exert a key role in the adult brain by promoting learning and memory [75]. Moreover in a dietary MetSyn-VCI model, gallic acid, a polyphenol and antioxidant present in grapes and green tea [76] improved recognition memory and increased hippocampal dendritic spine numbers by reducing the oxidative and inflammatory environment [77].

Evidence suggests that there are effects of physical exercise on neuroplasticity, learning and memory and investigations in preclinical models of MetSyn-VCI have produced very positive results [78, 79]. In CCAO rats modelling vascular dementia, exercise has demonstrated improvement in passive avoidance memory [80] and novel object recognition memory [51•] and increases in synaptic plasticity markers in the hippocampus and prefrontal cortex [51•, 81]. Environmental enrichment, a combination of voluntary exercise with stimulated surroundings and social interaction, alleviates memory impairment [82, 83] induced by CCAO and attenuates astrocyte activation and increases microvessel length in the hippocampus [82, 83]. Transcranial direct current stimulation (tDCS) has also been shown to stimulate increases in neuroplasticity and hippocampal long-term potentiation [84], the molecular basis of memory [85]. In a CCAO rat model, tDCS significantly alleviated the decreased hippocampal protein levels of IL-1 β , IL-6 and TNF- α and memory impairment observed in the Morris water maze [54].

Conclusion

Using models of MetSyn, VCI and VD researchers show cognitive and pathological deficits that model what is observed in humans. Promising reversal of these deficits is observed with environmental interventions, anti-inflammatory agents and antioxidants, although whether this can be replicated in patients is still to be seen. What is evident from the latest studies is that an expansion of focus is required. Interestingly, Ward and colleagues suggest that when investigating the hippocampus's role in VCI, we should consider it as a conceptual neurovascular unit which is composed of neurons, endothelial cells and glial cells, assessing the interaction between vasculature and the surrounding brain cells rather than neurons alone [52•]. This concept is repeated by Smith et al. [86] when we advance to clinical trials who suggest that future clinical trials should investigate the broad range of interventions in preclinical models including

oxidative stress and inflammation pathobiology to target the neurovascular unit in patients.

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Declarations

Conflict of Interest The author declares no competing interests.

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