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Abstract
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Vascular pharmacotherapy and dementia

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ABSTRACT

The incidence of dementia is increasing dramatically with the ageing population. Increasing evidence indicates that vascular disease is associated with cognitive decline and with the most common form of dementia, Alzheimer's disease (AD). Cardiovascular risk factors such as hyperlipidaemia, hypertension and type 2 diabetes have attracted attention as potential targets in the prevention of dementia. The present review aims to provide a concise overview of the recent advances linking vascular disease with dementia (with a particular focus on AD) and to examine the evidence for efficacy, where possible, for utilising vascular pharmacotherapy as a treatment option for dementia.
Introduction

An overview of dementia

The world population is getting older. The trend has accelerated over recent decades because of two main contributing factors: increased life expectancy due to improved medical knowledge and a continuing decline in birth rates (particularly in developed countries). Current estimates indicate that over half a billion people are aged over 60 years, a number predicted to double by 2030 [1]. It is further estimated that nearly 25 million people currently have dementia and this number is predicted to treble by 2040 [2]. Prevalence studies consistently show a doubling in dementia cases every 5 years from age 60, from about 1% at age 60-65 to over 40% at age 90 years. The incidence of dementia is also rising exponentially from the same age to reach 70 new cases per 1000 person-years in the oldest old [3,4]. Population ageing is a worldwide phenomenon and its associated dementia epidemic clearly has important public health implications.

Dementia is a progressive neurodegenerative brain disorder with many clinical presentations caused by multiple possible underlying aetiologies, rather than a unitary disease. Current clinical diagnostic criteria for the major dementia syndromes emphasize the following essential features: (i) development of multiple cognitive disturbance that may include memory impairment, aphasia (loss of the ability to articulate ideas or comprehend spoken or written language), apraxia (loss of the ability to perform coordinated movements or manipulate objects in the absence of motor or sensory impairment), agnosia (the inability to recognize common objects, persons, or sounds, in the absence of perceptual disability) or executive dysfunctions, (ii) the cognitive deficits of sufficient severity to cause impairment in occupational or social functioning, and, (iii) the cognitive deficits must represent a decline from a previously higher level of functioning. Underlying these definitions is the progressive
nature of dementia. In the population of people over the age of 65, Alzheimer’s disease (AD) accounts for up to two thirds of all cases of dementia. Together with vascular dementia (VaD) and dementia with Lewy bodies, they account for about 90% of all dementia cases. In dementia cases with onset before the age of 65, frontotemporal dementia (FTD) is the second most common form after AD. The typical clinical presentation of each dementia type depends on the location of the predominant pathology; memory in AD, executive function and speed of information processing in VaD, movement control and executive function in dementia with Lewy bodies, and behaviour and/or language in FTD.

It is important to note that significant clinical overlap exists across dementia types. About a third of AD patients present with significant executive dysfunctions and others exhibit early language disturbance, rather than the typical memory deficit [5-7]. Similarly, some FTD patients show early and severe episodic memory deficits [8]. As such, a proportion of patients who meet clinical criteria for one dementia type (e.g. AD) will also meet clinical criteria for a second, or even a third, dementia syndrome. It is also recognised that concordance between clinical diagnosis and neuropathology remains suboptimal. For example, a proportion of patients show brain pathology at postmortem that is different to their clinical diagnosis, or show multiple pathologies [9,10]. Adding further complexity to the clinical diagnosis, mixed presentations due to co-existing pathologies become more common with increasing age [11,12].

**Familial dementia**

Most cases of dementia are sporadic with no clearly identified aetiology. In about 10% of cases, however, genetic mutations causing dementia, in particular AD and FTD, have been
identified. In AD, causative mutations have been identified in the amyloid precursor protein, presenilin-1 and presenilin-2 genes [13-16]. Mutations in the tau, progranulin, as well as a couple of less frequent genes are associated with FTD [17]. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with VaD and caused by mutations on the notch 3 gene [18]. Approximately 10% of AD cases are thought to be genetically determined whereas 20-50% of all cases of FTD are estimated to be caused by gene mutations transmitted in an autosomal dominant fashion [19]. It is also clear that other cases with a strong family history of dementia exist without the known mutations. These families, affected over several generations, suggest the contribution of other genes as yet to be determined or other modes of genetic transmissions.

**Vascular risk factors and dementia**

Epidemiological studies have identified a number of risk factors associated with increased risk of sporadic forms of dementia, with age remaining the strongest predictor of most common forms of dementia. Additional dementia risk factors identified are associated with diabetes, cardiovascular disease, the metabolic syndrome and cerebrovascular disease and these include hypercholesterolaemia, hypertension, obesity, smoking, high alcohol consumption and high saturated fat intake [4,20]. There is mounting evidence that the presence of a number of these risk factors during midlife is predictive of increased dementia risk in later years [20-24]. Given that there is currently no curative or disease-modifying treatment for the major causes of dementia (i.e. AD and VaD), treatment of the vascular risk factors in order to reduce dementia risk or delay its onset represents a plausible approach to reduce the burden of disease. Lifestyle changes (e.g. smoking cessation, dietary change, increased physical activity, reduced alcohol consumption) are the most obvious preventive measures; however, these changes are not always easy to achieve. A number of
pharmacological/bioactive agents aimed at reducing vascular risk factors have recently been suggested as potential options for the prevention of dementia; these are summarised below.

**Hypertension – antihypertensive therapies**

Results from independent studies indicate that midlife hypertension is associated with increased risk for the development of cognitive impairment and dementia later in life [25,26]. It is well established that hypertension is associated with atherosclerosis of larger vessels and hypertensive subjects with cerebrovascular disease have an increased risk of recurrent stroke. Evidence indicates that hypertension also impacts on small blood vessel integrity, by reducing the resistance of the arteriole wall which will predispose to rupture and result in cerebral haemorrhage and concomitant cerebral damage (i.e. small vessel disease). In addition, it is likely that hypertension induces cognitive decline in the elderly due to its prolonged negative effect on cerebral arterial luminal diameter which results in hypoperfusion. This effect is greatest in brain regions fed by distal branches (e.g. deep brain nuclei, hippocampus, watershed areas), some of which are critical for memory function. These conditions could also contribute to cognitive decline and dementia. Based on the association of hypertension with dementia and the postulated mechanisms that may explain this link, the effects of blood pressure lowering on the development of cognitive impairment and dementia has been addressed in several studies. Recent studies indicate that blood pressure lowering reduces the risk of cognitive decline and dementia associated with recurrent stroke in patients with cerebrovascular disease [27]. In contrast, a systematic review of studies of blood pressure lowering in 12,091 hypertensive patients without apparent prior cerebrovascular disease concluded that there was no convincing evidence that blood pressure lowering prevents the development of cognitive impairment or dementia [28]. Two excellent recent reviews on this subject highlight the potential for variables, such as the type and combination of
antihypertensive treatment, the level of hypertension reduction (which can involve overshooting and concomitant problems with raised limits of cerebral autoregulation) and comorbidities, such as renal insufficiency, to influence the study outcomes related to dementia [26,29]. Although it is clear that anti-hypertensive treatment can prevent the development of cognitive impairment under specific circumstances, more detailed studies are require to confirm which patient groups and what types of medications are appropriate.

Lipid metabolism – cholesterol, statins and n-3 polyunsaturated fatty acids (PUFA)

In vitro studies and work in animal models suggest that cholesterol homeostasis has an impact on pathways that may ultimately regulate the cerebral concentration of the Alzheimer’s disease amyloid-β (Aβ) peptide [30-33]. Earlier epidemiological studies suggested an association between high serum cholesterol levels and an increased AD risk [34,35]; however, it was also shown that hypercholesterolaemia was associated with protection for dementia (including AD) in the elderly (>75 years) [36]. A systematic meta-analysis demonstrated a consistent association between high midlife (but not late-life) cholesterol levels and increased risk of AD and dementia of any type [37]. In addition, retrospective studies revealed a possible reduction in AD/dementia risk in association with use of the cholesterol-lowering statins [38,39] as well as a lower burden of neurofibrillary tangles and neuritic plaques (both are typical features of AD pathology) in post-mortem neuropathologic assessment [40]. Intriguingly, it has also been noted that statin use is associated with lower dementia risk independent of its cholesterol lowering effects [38]; thus the mechanism underlying this protection is still not clear. Data from prospective studies have so far not provided a clear answer regarding the use of statins as a preventive measure for AD; however, very recent results from a 9-year study, indicate that use of either lipophilic or non-lipophilic statins (but not non-statin cholesterol lowering drugs) was associated with a lower risk of AD (see [41]
and references cited therein). This study reinforces the idea that statins may protect against AD independently of their impact on serum cholesterol levels. In another recent study examining the pleiotropic effects of statins in multiple diseases, a protective effect against dementia was observed [42]. The majority of cases were diagnosed with VaD or unspecified dementia and the protective effect was similar for AD and non-AD dementia [42].

It is also important to mention that statins prevent stroke and may decrease cerebral damage if therapy is initiated within 24 h of onset of acute ischaemic stroke [43,44]. These effects are likely to be mediated at least partially by stabilisation of vulnerable atherosclerotic plaques in the aorta and carotid artery thereby reducing the risk of thromboembolism; although several pleiotropic effects (including antithrombotic actions and direct actions that improve endothelial function, e.g. increasing nitric oxide bioavailability) have also been postulated [43,44]. It is also conceivable that statins may afford protection in the setting of “multi-infarct dementia” where multiple cerebral microinfarcts may lead to cerebral hypoperfusion which has been suggested to contribute to cognitive decline in normal brain ageing, VaD and AD [45-49]. We are not aware of studies that have directly investigated the effect of statin treatment on cerebral microinfarct formation but this would seem to be an important area to investigate. While more research is required, it appears that statins may yet provide a plausible therapeutic option to reduce risk for AD and possibly VaD and other non-AD dementias. Other studies related to cholesterol homeostasis and AD, have revealed that enzymatically oxidised forms of cholesterol (oxysterols), and synthetic compounds that activate the nuclear hormone receptor LXRα, inhibit cerebral Aβ accumulation in animal studies and it is predicted that compounds that may regulate LXRα-inducible genes to treat AD in humans may follow [50].
Another area of lipid metabolism that has been the focus of several studies related to preventive strategies for dementia involves the administration of n-3 PUFA that are present at high concentrations in fish oils. Epidemiological studies, both cross-sectional and longitudinal, have yielded conflicting results regarding an association between n-3 PUFA consumption and cognitive decline (see [51,52] and references cited therein). In recent short term (6 months) randomised, double-blind, placebo-controlled studies of AD patients or normal elderly subjects, supplementation with n-3 PUFA (up to 1.8 g/day) did not result in marked improvements in neuropsychiatric symptoms in the patients or in enhanced cognitive performance in the cognitively healthy elderly subjects [52,53]. Although it appears that n-3 PUFA supplements may not be helpful, at least in the short term, previous studies have reported that high concentrations of n-3 PUFA in the blood is associated with a lower risk of cognitive decline [54-56]. This may be associated with long-term anti-inflammatory actions (e.g., decreased production of pro-inflammatory cytokines from peripheral blood mononuclear cells) or blood pressure lowering effects in hypertensive subjects that would be predicted to decrease the risk of cognitive decline and potentially reduce the risk of developing AD in specific sub-groups of the population [57].

**Type 2 diabetes - peroxisome proliferator-activated receptor gamma (PPARγ) agonists and insulin**

Subjects with non-insulin-dependent diabetes mellitus (commonly referred to as type 2 diabetes) in the Rotterdam Study were found to have a 3-fold increased risk of developing dementia [58]. Although this risk was strongly associated with VaD, similar associations were also observed for AD [58]. It has also been reported that diabetes in midlife is a strong predictor of dementia later (3 decades) in life [59]. Several epidemiological studies have now confirmed an association of type 2 diabetes (and its precursor, insulin resistance syndrome)
with increased risk for VaD and AD (see [60] and references cited therein). Interestingly, in a study of twins in which the possible association of multiple vascular risk factors (diabetes, hypercholesterolaemia, hypertension and elevated body mass index) with cognitive decline was examined, only diabetes was significantly correlated with accelerated cognitive decline [61]. As discussed in detail by Biessels and Kapelle [62] and Martins et al. [60], diabetic cerebrovascular disease and abnormal cerebral glucose utilisation have been implicated as causative factors in AD associated with type 2 diabetes. In addition, pathological studies in humans have demonstrated increased microvascular infarcts in dementia patients with diabetes compared with dementia patients without diabetes [63]. Strong evidence from animal studies (streptozotocin-treated rats) shows that diabetes progressively increases blood-brain barrier (BBB) permeability [64]. Insulin treatment appears to be a useful approach to resolve in part the altered BBB permeability in the early stages of disease in the rat model [64].

Increased BBB permeability may also be related to cerebral microvascular pathology in humans [64,65]. In diabetic patients with dementia, however, treatment of hyperglycaemia (with insulin and/or sulfonylureas and/or metformin) increased the number microvascular infarcts in deep cerebral structures when compared with untreated diabetic patients with dementia [63]. Magnetic resonance imaging (MRI) has provided further evidence for vascular damage (infarcts, lacunes and white matter hyperintensities) associated with type 2 diabetes in the Honolulu-Asia aging study [66]. Additional studies focusing on the impact that specific anti-hyperglycaemic treatments may have on human microvascular pathology are required to clarify the complex association of diabetic microvascular/BBB dysfunction with dementia.

Largely based on epidemiological evidence, additional therapies that are used to treat type 2 diabetes are under investigation for their protective potential in AD. The major therapeutic approach under examination in this context is the thiazolidinedione (TZD) class of
compounds that are agonists for the nuclear receptor, PPARγ [67]. PPARγ agonists regulate lipid metabolism, energy metabolism, insulin sensitivity and may also act as anti-inflammatory agents and modulators of Aβ production and/or clearance [67-69]. There is strong evidence that the PPARγ agonist rosiglitazone enhances attention and memory in patients with mild to moderate AD [70]. Intriguingly, patients possessing an apoE4 allele do not gain therapeutic potential from rosiglitazone [70]. More specifically, using the Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-Cog) score as a primary efficacy endpoint, APOE ε4-negative patients showed improvement in cognitive function after 24 weeks of rosiglitazone treatment whereas APOE ε4-positive patients showed no improvement overall [70]. The precise mechanism(s) by which TZDs may improve memory and cognition in dementia patients remains an open question. Pioglitazone is thought to pass the BBB to some degree while rosiglitazone is suggested to mediate its protective effects in the peripheral circulation, although there is some evidence from mouse studies to suggest small amounts of rosiglitazone may also enter the brain (see [67] and references cited therein). In addition to the possible beneficial effects of TZDs on insulin sensitivity, inflammation and Aβ homeostasis, peripheral lipoprotein metabolism is also targeted. In this context, pioglitazone and rosiglitazone appear to have quite distinct effects with pioglitazone treatment associated with significant improvements in plasma triglyceride, HDL cholesterol and LDL particle size and concentration as compared with rosiglitazone [71,72]. Potential differences in TZD efficacy related to memory and cognition in humans remains to be established. Studies are currently underway that will shed further light on this promising approach (14 clinical trials listed, 13 using rosiglitazone and one using pioglitazone, at the US clinical trials website [www.clinicaltrials.gov] at the time of writing).
It has also been proposed that insulin resistance may play a direct role in AD [60,73]. Diabetic complications associated with cerebrovascular accumulation of advanced glycation end products (AGEs) represent one plausible explanation for this association. Another more direct mechanism involves a role for insulin in CNS energy metabolism. For example, insulin-sensitive glucose transporters are expressed in brain regions that are associated with memory and learning and insulin treatment can profoundly modulate cognitive function under experimental settings [74,75]. In order to examine the direct impact of central insulin administration on memory, recent studies have assessed the impact intranasal insulin delivery has on cognitive function in humans [76-78]. The data indicate that intranasal insulin administration may improve attention in patients with early AD or mild cognitive impairment and that verbal memory may also be improved but only in subjects who do not carry an apoE4 allele. Interestingly, subjects who carry an apoE4 allele demonstrated a relative decline in verbal memory with insulin administration [77]. Clearly, further studies are required to confirm which patient groups would benefit from intranasal insulin administration.

Cerebrovascular inflammation – nonsteroidal anti-inflammatory drugs (NSAIDs)

Cortical neuroinflammation is a key feature of AD and increased levels of luminal Aβ may permeabilize the blood-brain barrier (BBB), increasing vasoconstriction of arterial vessels, and thereby contributing to chronic inflammation [79]. Cerebral amyloidosis is highly prevalent in AD and VaD and it has been suggested that anti-inflammatory medications may alleviate these problems [80-83]. Several epidemiological studies have shown that the prevalence of AD is reduced in people using NSAIDs (see [81,84-86] and references cited therein). Interestingly, the protective effect of NSAID use appears to be observed only in subjects who carry an apoE4 allele [85]. Based on the epidemiological studies and the
demonstrated anti-amyloidogenic actions of specific NSAIDs in animal studies (e.g. [81]), a number of prospective studies aiming to assess the efficacy of NSAIDs in the prevention of AD or slowing of cognitive decline in persons at risk of developing dementia have been undertaken. Unfortunately, the results from a large randomised, controlled trial of the NSAIDs naproxen and celecoxib have shown that anti-inflammatory treatment did not improve cognitive function in subjects with a family history of AD and the final recommendation was that these specific anti-inflammatory agents should not be used for the prevention of AD [87]. It is possible that the follow-up period (1 to 4 years) was not sufficient to detect a benefit in this study (i.e. since AD has a long sub-clinical phase in which exposure of a preventative therapeutic may be required). Alternatively, because there was weak evidence for a detrimental effect of naproxen [87], it maybe that neuroinflammation demonstrated by microglial activation maybe beneficial in terms of responding appropriately to Aβ deposition and clearance [88].

**Vitamin supplements**

Several lines of evidence led to the proposal that dietary supplementation with vitamin C, vitamin E or the B group vitamins, folate, B₆ and B₁₂, may reduce cognitive decline in the elderly and afford protection for AD [89-91]. In general, the potential protective action of vitamins C and E is speculated to be via reduction of oxidative stress that is associated with AD [92]; whereas the B vitamins are predicted to offer benefit by reducing the concentration of the potentially harmful amino acid homocysteine [90]. Epidemiological studies suggest an association between AD risk and low plasma levels of vitamin E and high levels of homocysteine [93,94]. Very similar proposals for antioxidant vitamin supplementation and homocysteine reducing strategies have been suggested for the treatment of vascular diseases including atherosclerosis [95]. It now seems that neither antioxidant vitamin supplements or
reductions in plasma homocysteine concentrations provide a general benefit for vascular disease [96-99]. Emerging data also suggest that supplementation with these vitamins may not be useful for the treatment of dementia. Prospective trials and meta-analyses of the literature failed to detect consistent therapeutic benefits with vitamin E and vitamin C supplementation in terms of risk for developing AD and non-AD dementia [100-102]. Similarly, recent data suggest that supplementation with B group vitamins to reduce plasma homocysteine levels does not have an impact on cognitive decline or AD [103-106]. Although it remains possible that in vitamin deficient states, dietary supplements may provide some benefit, it is becoming increasingly clear that dietary supplementation with the abovementioned vitamins does not offer a therapeutic benefit for the prevention of cognitive decline or AD.

**Conclusions**

There is substantial epidemiological data indicating that vascular disease may be causative in dementia including AD. In addition, risk factors for both peripheral and microvascular diseases (including atherosclerosis and hypertension) and diabetes also increase risk for AD. Advances in the development of biomarkers (e.g. using brain imaging techniques) for cerebrovascular disease continues to provide insights into the complex interplay between vascular disease and both AD and non-AD dementia [107,108]. Despite strong rationale for therapeutic targeting of vascular disease/vascular risk factors as a potential strategy to prevent the onset of AD or at least slow cognitive decline in the elderly [109-113], prospective studies so far have not generally supported the idea that vascular pharmacotherapy can be considered as an efficacious option for the treatment or prevention of dementia in the general population. It is clear, however, that certain sub-populations may indeed benefit from some of the therapies (e.g. subjects who do not posses an apoE4 allele benefit from rosiglitazone and from intranasal insulin administration). It may also be the case that timing and duration of
therapeutic administration is the key to success since AD and non-AD dementias are thought to have a long sub-clinical phase (i.e. sometimes 20 years or more). Although it appears that there is no vascular panacea that will help in the fight against the increasing prevalence of dementia, the current evidence indicates that specific sub-groups in the population will benefit from selected vascular pharmacotherapies and the challenge now is to define accurately the genetic, age and risk-factor profiles of those individuals who will benefit from such intervention.

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