Vascular and Metabolic Factors in Alzheimer's Disease and Related Dementias: Introduction

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Dementia, a progressive and irreversible cognitive deterioration typically associated with aging, has recently been recognized as one of the major health challenges of our century (Holtzman et al. 2011). There are ≈ 40 million people suffering from dementia in the world, a number estimated to triplicate by 2050 due to the aging of the world population and the lack of effective treatments (Prince et al. 2013). The realization that the world will soon be faced with a dementia epidemic has led to national and international efforts to develop strategies to curb its devastating socioeconomic impact (Alzheimer's Association National Plan Milestone Workgroup et al. 2014; World Health Organization 2012).

The two major causes of dementia are Alzheimer's disease (AD), responsible for 70–80 % of cases, and dementia caused by vascular factors (Gorelick et al. 2011; Prince et al. 2013). AD is characterized neuropathologically by the presence of extracellular deposits of an amyloid substance (amyloid plaques) and intraneuronal aggregates of the microtubule-associated protein tau (neurofibrillary tangles) (Masters et al. 2015). The main component of amyloid plaques is amyloid- β (A β), a 40–42 aminoacid peptide cleaved from the amyloid precursor protein (APP) by α - and β -secretase enzymes (Masters et al. 2015).

Cognitive impairment on vascular basis is caused by a wide variety of ischemic lesions. Multiple infarcts affecting several brain regions (multi-infarct dementia) or a single

infarct in areas involved in cognition (strategic infarct dementia) are well established but rare causes (Iadecola 2013); rather, cognitive impairment on vascular basis results most commonly from discrete or confluent white matter lesions (white matter disease) caused by alterations of small arterioles of the basal ganglia and subcortical white matter (small vessel disease) (Gorelick et al. 2011). The term vascular cognitive impairment (VCI) refers to all the cognitive manifestation of cerebrovascular diseases, whereas “vascular dementia” indicates the most extreme case of VCI, in which multiple cognitive domains are affected interfering with day-to-day activities (Gorelick et al. 2011).

AD and VCI were traditionally considered distinct pathophysiological entities, AD being caused by neurodegeneration driven by A β and tau (Hardy 2006), and VCI caused by cerebral ischemia due to pathological changes in arterioles, i.e., arteriosclerosis, lipohyalinosis, and fibrinoid necrosis (small vessel disease) (Pantoni 2010). However, increasing evidence indicates that there is much overlap between these two conditions (Iadecola 2010). First, epidemiological studies have indicated that clinically diagnosed AD and VCI share common risk factors, such as hypertension, obesity, diabetes, etc., suggesting the involvement of common pathogenic factors (Casserly and Topol 2004). Second, community-based pathological studies have revealed that AD and cerebrovascular lesions coexist in 40–50 % of clinically diagnosed AD, making mixed AD-vascular dementia the most common cause of cognitive impairment in the aged (Schneider et al. 2007; Sonnen et al. 2007). Third, several studies have demonstrated that cerebral blood flow (CBF) and its reactivity to vasoactive stimuli are reduced in patients with AD-type dementia, effects observed even in the presymptomatic stages of the diseases (Binnewijzend et al. 2015; Cantin

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et al. 2011; Iadecola 2013; Ruitenberg et al. 2005). Fourth, pathological studies have revealed an intriguing interaction between small basal ganglia ischemic lesions and AD pathology, such that their coexistence greatly amplifies the expression of the cognitive deficits beyond what would be expected based on the AD pathology alone (Esiri et al. 1999; Snowden et al. 1997). These observations have suggested that vascular factors may play a role not only in VCI, but also in the development and evolution of AD (Iadecola 2004).

Experimental studies in mouse models overexpressing mutated forms of APP and exhibiting brain A β accumulation have corroborated these clinical–pathological findings. A β is a potent vasoconstrictor (Niwa et al. 2001; Thomas et al. 1996), reduces resting CBF (Niwa et al. 2002b) and attenuates the increase in CBF induced by endothelial cells (endothelium-dependent vasodilatation) and neuronal activation (functional hyperemia) (Iadecola et al. 1999; Niwa et al. 2000), key mechanisms regulating the cerebral circulation. Furthermore, A β impairs cerebrovascular autoregulation, a fundamental response of the cerebral circulation that maintains CBF relatively independent of arterial pressure over a certain range (Niwa et al. 2002a). These alterations in neurovascular regulation reduce the cerebral blood supply and increase the susceptibility of the brain to cerebral ischemia (Zhang et al. 1997). Importantly, these vascular abnormalities are observed in the absence of deposition of A β in amyloid plaques or around cerebral blood vessels (cerebral amyloid angiopathy), suggesting that soluble or oligomeric A β is the vasotoxic species. The cerebrovascular effects of A β are mediated in large part by activation of the free radical-producing enzyme NADPH oxidase through the innate immunity receptor CD36, and are reversible by pharmacological or genetic approaches to scavenge radicals or block their production (Han et al. 2015; Iadecola et al. 1999; Nicolakakis et al. 2008; Park et al. 2013, 2008). However, these neurovascular alterations become irreversible in advanced disease, due to accumulation of A β in cerebral blood vessels which leads to damage to endothelium, smooth muscle cells, and pericytes (Park et al. 2013, 2014). Collectively, the evidence to date suggests that A β , in addition to its well-established effects on synaptic function, also targets cerebral blood vessels leading to neurovascular dysfunction and lowering the threshold for cerebral ischemic injury. In support of this hypothesis, patients with AD are at greater risk for stroke (Chi et al. 2013; Tolppanen et al. 2013).

Additional evidence linking vascular factors to the pathogenesis of AD was provided by studies demonstrating that the cerebral vasculature is critical for the removal of A β from the brain. A β is produced normally during neural activity (Cirrito et al. 2005), but is promptly cleared from

the extracellular space to prevent its accumulation. Indeed, failure of A β clearance has emerged as a culprit in sporadic cases of AD (Mawuenyega et al. 2010). Brain A β clearance is thought to rely on parenchymal and vascular mechanisms (Miners et al. 2014). In addition to parenchymal enzymes that degrade A β (neprilysin, insulin degrading enzyme, plasmin, and endothelin converting enzyme) (Miners et al. 2008), A β is removed (a) through perivascular pathways draining into the cervical lymph nodes (Tarasoff-Conway et al. 2015), and (b) by binding vascular transport receptors (LRP1, PICALM) and crossing the vascular wall to reach the circulation (Shibata et al. 2000; Storck et al. 2015; Zhao et al. 2015). A paravascular pathway involving astrocytic end-feet (glymphatic system), which has the potential to clear A β from the brain (Iliff et al. 2012), has been recently discovered and could play a role. Cerebrovascular damage prevents A β removal and leads to amyloid accumulation in brain and vessels (Faraco et al. 2015; Park et al. 2013). Therefore, the health of the cerebral vasculature is critical for A β clearance, and vascular damage is likely to promote amyloid deposition also in AD.

In this special issue of *Cellular and Molecular Neurobiology*, leading experts in the field address some of the key questions still outstanding concerning the role of vascular factors and AD pathology on cognitive health. The contributions span from the effects of A β on cerebrovascular regulation and cognitive function to the mechanisms of A β clearance and their failure in AD. The intriguing relationship between AD and regulation of body weight and metabolism is also examined. In addition, novel therapeutic approaches focusing on both parenchymal and vascular targets are examined. Data are presented on the reduction in CBF and on enlargement of perivascular space as diagnostic tools and potential biomarkers of early disease.

Other contributions focus on the cerebrovascular effects of risk factors linked to cognitive impairment, such as hypertension and diabetes, and on much needed animal models of VCI. The role of the blood–brain barrier is examined in the context of the cerebrovascular damage produced by hypertension, the major cause of VCI and a risk factor for AD as well. Based on the weight of the evidence, the rationale for advancing research priorities in vascular contributions to cognitive decline is also articulated.

Overall, these contributions provide a glimpse into the changing landscape of dementia research, which has shifted from an exclusive focus on neurodegeneration to a more balanced view implicating vascular factors, either independently or in concert with AD pathology, in the development and/or expression of cognitive decline (Snyder et al. 2014). The body of work presented in this issue

supports the emerging notion that, in the absence of mechanistic treatments for dementia, maintenance of vascular and cognitive health is the best available option to contain the catastrophic societal and economic impact of the upcoming dementia epidemic (Iadecola 2013; Kuehn 2015).

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