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Mini Review

Cerebral autoregulation in Alzheimer's disease

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Cerebral autoregulation aims to stabilize blood flow to the brain during variations in perfusion pressure, thus protecting the brain against the risks of low or high systemic blood pressure. This vital mechanism is severely impaired in the transgenic mouse model of Alzheimer's disease (AD) that abundantly produces amyloid-β peptide β_{1-42}. These observations have been extrapolated to human AD, wherein impairment of autoregulation could have important implications for the clinical management and prevention of AD. Research on cerebral autoregulation in human AD, however, has only recently become available. Contrary to the animal models, preliminary studies suggest that cerebral autoregulation is preserved in patients with AD. Further research is urgently needed to elucidate this discrepancy in the current literature, given the accumulating evidence that implicates cerebrovascular pathology in AD.
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Introduction

The current paradigm regards Alzheimer's disease (AD) as a disorder with progressive loss of synapses, neuronal death, and dysfunction due to the toxic effects of accumulation of amyloid-β_{1-42} peptides (Aβ) and neurofibrillary tangles (Querfurth and LaFerla, 2010). Rare cases of familial AD, with genetic mutations that lead to overproduction of Aβ, provide strong support for this amyloid hypothesis. Although most work on AD has considered neurons as an isolated entity, more recently attention has broadened to include the interactions between neurons, glia, vasculature, and perivascular tissue—collectively termed as the neurovascular unit (Iadecola, 2004). The importance of this interaction between the vasculature and neurons was stressed by epidemiologic studies that identified risk factors for AD to be similar to those for cardiovascular disease (Breteler, 2000). The notion that AD affects not only neurons but also the neurovascular unit as a whole, became clear when immunotherapy targeted against Aβ in AD patients elicited strong inflammatory responses in cerebral blood vessels, uncovering both glial and vascular involvement in AD pathology (Pfeifer *et al*, 2002).

This relationship between the cerebral vasculature and AD is likely to be bidirectional. Cerebrovascular disease, through chronic hypoperfusion and oxidative stress, modulates neuronal overproduction of Aβ and may thus initiate or aggravate AD pathology (Kalaria, 2000, 2009; Claassen, 2008; Austin *et al*, 2010). Alzheimer's disease, in itself, may lead to vascular disease, as neuronal overproduction of Aβ exerts detrimental effects on cerebrovascular function (Thomas *et al*, 1996).

Cerebral autoregulation, the mechanism that aims to stabilize blood flow to the brain in the context of changes in cerebral perfusion pressure (van Beek *et al*, 2008), serves as an important illustration of this complex interaction between AD and vascular function: AD-related vascular pathology may impair cerebral autoregulation and lead to cerebrovascular insufficiency, which in turn may contribute to the

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progression of AD. In this review, we will discuss recent advances in our understanding of the relationship between cerebral autoregulation and AD. From a clinical perspective, if AD impairs autoregulation, AD patients will be more vulnerable to the disruption of cerebral hemodynamic homeostasis, bearing a wide array of clinical consequences. For example, impaired autoregulation in preclinical AD, if combined with blood pressure instability, may accelerate AD progression. In addition, bearing in mind that most patients with sporadic AD are older and have vascular comorbidity, such as hypertension and diabetes, it is plausible that unrecognized interactions between cerebral hemodynamics and neuronal function underlie the failure of many experimental therapeutics that are based solely on the amyloid hypothesis (Pimplikar, 2009).

Terminology

The term cerebral autoregulation has been used less discriminatory by some authors to encompass neurovascular coupling, or vasomotor reactivity to arterial CO_2, instead of its classic definition of the pressure–flow relationship of the cerebral circulation (van Beek *et al*, 2008). It is important to have a clear understanding of the underlying physiologic processes that may go awry if the neurovascular unit dysfunctions, and of the terminology used to describe these processes.

Neurovascular coupling describes the process in which activation of a brain region evokes a local increase in blood flow. Although the exact mechanisms remain the subject of further study, one hypothesis is that astrocytes (glia) have a key role as intermediary between neurons and blood vessels (Hamel, 2006), for review see Attwell *et al*, (2010).

Vasomotor (or vascular) reactivity refers to the vasodilatory or vasoconstrictor responses of cerebral blood vessels to hypercapnic or hypocapnic stimuli, in other words, global or regional brain blood flow responses to systemic changes in arterial [CO_2] (Claassen *et al*, 2007). Of note, local brain metabolic changes in [CO_2] likely have a minimal role in cerebral blood flow (CBF) response to brain activation (Lin *et al*, 2010), suggesting that neurovascular coupling and vasomotor reactivity to CO_2 may be mediated by different regulatory mechanisms.

Cerebral autoregulation describes the pressure–flow relationship of the cerebral circulation under both dynamic and steady-state conditions. Cerebral autoregulation and vasomotor reactivity to CO_2 are often confused, but are different processes. The distinction between vasomotor reactivity and autoregulation is exemplified by the fact that these properties may be dissociated in the same individual (Lavi *et al*, 2006). In this review, the term cerebral autoregulation exclusively stands for the cerebrovascular response to changes in perfusion pressure.

Cerebral autoregulation in animal models of Alzheimer's disease

Strong evidence for impairment of cerebral autoregulation by AD was derived from animal studies. In transgenic mice that overexpress mutated human *amyloid precursor protein* genes, which abundantly produce Aβ, basal CBF was reduced, endothelium-dependent vasodilatation was impaired, and vasoconstrictor responses were exaggerated. These changes were present already at young age, before the occurrence of Aβ deposition in brain parenchyma (Iadecola *et al*, 1999). Consequently, cerebral autoregulation was found to be profoundly impaired (Niwa *et al*, 2002). These observations confirmed the earlier work that had demonstrated that Aβ was 'vasotoxic' (Thomas *et al*, 1996).

Also, Aβ may affect vascular function by blocking neurogenic vascular control, as it is toxic to basal forebrain cholinergic neurons (Tong and Hamel, 1999; Claassen and Jansen, 2006; Hamel, 2006). Disruption of these cholinergic projections to intracerebral microvessels could impair vasodilatory responses in AD (van Beek and Claassen, 2010). In addition to the effects mediated by Aβ, *in vitro* studies revealed that vascular smooth muscle cells in AD display enhanced expression of factors (serum response factor and myocardin) that promote a hypercontractile state and may thus contribute to reduced cerebral perfusion (Chow *et al*, 2007). Finally, added to all these functional vascular changes, cerebral vascular architecture is severely distorted in *APP* mice (Meyer *et al*, 2008). Of note, the fact that these vascular changes occur in young animals, in the absence of notable brain Aβ deposition, is important as it suggests that vascular abnormalities are not merely a consequence of the neurodegenerative process—which *per se* could lead to reduced metabolic demand and secondary vascular changes.

In later stages of AD, both in mice and man, cerebrovascular depositions of Aβ are observed, mostly in the form of $A\beta_{1-40}$, known as cerebral amyloid angiopathy. Cerebral amyloid angiopathy gradually causes vascular smooth muscle degeneration, increases vessel stiffness and thus alters vascular function. Cerebral amyloid angiopathy also may block both the perivascular route and the blood-brain barrier route of Aβ drainage, which in turn contributes to further perivascular as well as brain parenchymal Aβ deposition (Weller *et al*, 2008).

Taken together, these observations build a strong case supporting a direct link between AD and cerebrovascular dysfunction. In recent literature, these findings from animal studies have often been extrapolated to clinical AD. However, data on cerebral autoregulation in AD patients are scarce. In the following section, we will review clinical research on this topic.

Cerebral autoregulation in Alzheimer's disease

Research that investigated cerebral autoregulation specifically in clinical AD has only recently become available, with the first such study published in 2009 (Claassen *et al*, 2009*a*). In a much earlier work, cerebral autoregulation was assessed in a small group of patients ($n = 9$) with unselected types of dementia (Simard *et al*, 1971). In this study, CBF responses to acute changes in arterial pressure were measured using the ^{133}Xe intra-arterial injection method. Acute changes in arterial pressure were induced either pharmacologically with intravenous infusion of angiotensin II or trimethaphan or during vasovagal attack under complicated clinical conditions. On average, CBF did not change during moderate changes in arterial pressure, suggesting that cerebral autoregulation was preserved. However, these observations are limited by the fact that no healthy, age-matched control subjects were enrolled and that the number of patients was too small in light of the pathologic complexity of dementia types included in this study (presenile, senile, vascular, Korsakoff psychosis, and post-infectious dementia).

A total of four studies on cerebral autoregulation in AD have been published since 2009, with their own limitations and strengths, which we will review below. Because they are complementary in methodology and approach, together these studies provide important new insights. In contrast, a much larger body of work has been devoted to the study of baseline CBF in AD (Breteler, 2000; Farkas and Luiten, 2001; Bateman *et al*, 2006), consistently demonstrating a reduction in regional perfusion that correlates in various degrees with cognitive impairment (for review see Farkas and Luiten (2001)). Although the cause of this reduced perfusion remains a subject for debate, a reduced metabolic activity related to neurodegeneration may have an important role (Matsuda *et al*, 2002; Matsuda, 2007; Yoshiura *et al*, 2009). The scope of this review, however, is not to discuss the cause or consequence of these steady-state hemodynamic changes, but to discuss the autoregulatory properties of the cerebrovascular bed to changes in perfusion pressure, and how these are affected by AD.

Positron emission tomography

Zazulia *et al* (2010) investigated 20 patients with mild AD (CDR 0.5 or 1). All patients met NINCDS-ADRDA criteria for probable AD. Using ^{15}O-positron emission tomography (PET), the authors measured changes in CBF following a step decrease in systemic blood pressure induced by intravenous infusion of the calcium-channel blocker nicardipine. The advantage of PET is its high spatial resolution. This allowed the authors to investigate both global and regional cerebral autoregulation. Moreover, cerebrovascular function was assessed in regions with evident Aβ pathology, using ^{11}C-PIB imaging as a marker of Aβ deposition. Contrary to the observations in the transgenic AD mice, which would have predicted a reduction in CBF, cerebral perfusion was well maintained in patients with AD despite a mean reduction in arterial pressure of 15 mm Hg (14% from baseline), both globally and in areas with high PIB uptake (high Aβ load). These data were interpreted to indicate normal cerebral autoregulation in AD. However, several limitations may have led to a false-negative finding. Most importantly, nicardipine was used to decrease blood pressure, through systemic vasodilation. The essence of any investigation of cerebral autoregulation is that the method used to alter blood pressure does not in itself affect the cerebral circulation. In this study, this prerequisite was not met. Nicardipine may have direct effects on the cerebral vasculature, as it led to vascular remodeling and cerebral vasodilatation in pial and intracerebral arteries in a rat model, and reduced cerebral vasospasm in patients with subarachnoid hemorrhage (Sabbatini *et al*, 2001; Nogueira *et al*, 2009). Thus, it is possible that the observed stability in CBF in response to reduced blood pressure was due at least partially to cerebral vasodilatation that was mediated directly by nicardipine. Of note, the authors chose this drug mainly for safety reasons, because in patients with established cerebrovascular disease and a high probability of impaired autoregulation, nicardipine lowered blood pressure without reducing CBF (Powers *et al*, 2009). Nonetheless, to ascribe their finding of normal autoregulation solely to nicardipine, we must make the assumption that this drug induced vasodilatation to a degree that matches exactly what would be needed to compensate for the reduction in perfusion pressure, and that this occurred equally throughout the brain, even in areas with high amyloid burden.

The second limitation is inherent to the method chosen to measure CBF. The advantage of high spatial resolution offered by PET comes at a price of low-temporal resolution, i.e., only averages of CBF over a time scale of several minutes can be quantified. When blood pressure falls, CBF may be proportionally reduced transiently, but then recovers to baseline values in the face of a sustained blood pressure reduction. In humans, both the magnitude of the initial decline in CBF and the time to recovery depend on the adequacy of the cerebrovascular response. The time span of this process is measured in 5 to 10 seconds, not minutes, and has been referred to as dynamic cerebral autoregulation. Clearly, this process was missed in the PET study. Study of these short-term dynamics of cerebral autoregulation is important in that blood pressure is dynamic in nature and fluctuates constantly in daily life. Thus, AD patients may experience a more profound decline in brain perfusion after hypotension, a prolonged time to recovery, or both, which may lead to transient brain ischemia affecting neuronal function. Finally, for steady-state

autoregulation, a 14% reduction in blood pressure from baseline may be too small to reveal changes in autoregulation as it may fall within the range of normal autoregulation (van Beek *et al*, 2008).

Transcranial Doppler

The study by Zazulia *et al* (2010) is complemented by three studies that specifically addressed the dynamic pressure–flow relationship in AD, using transcranial Doppler (TCD) to measure changes in CBF with high-temporal resolution (Claassen *et al*, 2009*a*; van Beek *et al*, 2010*a*, 2011). To avoid the conundrum of using vasoactive drugs to study cerebral autoregulation, blood pressure was altered non-pharmacologically. Fluctuations in pressure were brought about by changes in body posture, e.g., from sit to stand or squat to stand, thus simulating blood pressure changes as they occur in daily life (Claassen *et al*, 2009*b*).

In nine patients with mild probable AD, CDR 0.5 to 1, CBF velocity in the middle cerebral artery was measured using TCD, which allows to monitor changes in CBF on a beat-to-beat basis. A control group of eight subjects matched for age, sex, and educational levels was used for comparison. This study observed significant hemodynamic differences at baseline between AD and control subjects. That is, AD patients had lower CBF velocity, higher blood pressure and blood pressure variability, and higher cerebrovascular resistance. If AD patients have an impaired autoregulation, larger variations in CBF would be expected compared with controls. However, the contrary was observed: fluctuations in CBF in response to fluctuations in blood pressure were smaller in AD, which suggests that either cerebral autoregulation was not impaired or changes in CBF were attenuated by chronic cerebral vasoconstriction, as has been demonstrated in experimental models of AD (Chow *et al*, 2007; Weller *et al*, 2008). Limitations of this study are that the sample size is small and only global blood flow in one large territory (middle cerebral artery) was measured, leaving open the option that regional impairment of autoregulation was missed. In addition, these patients all used cholinesterase inhibitors, which may have affected cerebral autoregulation (Claassen and Jansen, 2006; Claassen *et al*, 2009*c*; van Beek and Claassen, 2010). However, these observations were confirmed in a different population of 21 patients with AD (CDR 1), studied before initiation of cholinesterase inhibitor therapy (van Beek *et al*, 2010*a*, *b*). Moreover, re-assessment during treatment showed no effect of cholinesterase inhibitors on dynamic autoregulation.

Near-infrared spectroscopy

Two studies used near-infrared spectroscopy (NIRS) to measure fluctuations in oxygenated hemoglobin in the frontal cortex of AD patients during rapid changes in CBF and blood pressure (van Beek *et al*, 2010*a*, 2011). Even though blood pressure and CBF responses (TCD) were comparable in AD and controls, frontal cortical oxygenation was more reduced during postural hypotension in AD. Transfer function analysis also showed a phase delay between oscillations in CBF and oxygenated hemoglobin in AD relative to controls. NIRS could be influenced by brain atrophy and reduced blood flow in AD, in that reduced blood flow would decrease hemoglobin concentrations and potentially reduce oscillations in oxygenated hemoglobin, whereas atrophy would reduce the amount of hemoglobin measured by the NIRS optodes. However, this was not the case in these studies.

These observations of apparently preserved autoregulation in AD measured with TCD, combined with subtle impairments in cortical tissue oxygenation, suggests that in clinical AD, vascular dysfunction may be primarily located in the microcirculation, including arterioles and/or capillaries, rather than in the larger blood vessels that are important for cerebral autoregulation (van Beek *et al*, 2011).

Conclusion

Three centers that have investigated a total of 50 AD patients from different populations were unable to show the severe impairment of cerebral autoregulation in AD that was expected based on observations in animal models. Their findings suggest preserved compensatory vascular mechanisms at the early stage of the disease to protect brain perfusion in the face of changes in systemic blood pressure. Diagnostic inaccuracy about AD cannot explain these negative findings, as each center had considerable expertize in diagnosing AD and all patients met NINCDS-ADRDA criteria for probable AD, as well as the more recent research criteria for AD (diagnoses were supported by imaging and cerebrospinal fluid biomarkers). In addition, there was no biased selection of young and cardiovascular fit patients, as a wide age range was spanned (60 to 80 years), and patients had vascular comorbidities (hypertension, diabetes), which, if anything, would enhance but not reduce the chance to find impaired autoregulation.

Both static (the PET study) and dynamic (the TCD and NIRS studies) autoregulation were investigated in these studies. The clinical relevance of static autoregulation lies primarily in understanding the effects of chronic reductions in blood pressure with antihypertensive treatment, whereas dynamic autoregulation is important to know the consequences of intermittent blood pressure reductions, e.g., during change in posture, which may also be affected by pharmacological treatment. It is therefore important that both aspects be studied, when possible in conjunction.

The controversial findings of cerebral autoregulation between patients with AD and the transgenic mouse model of AD highlight additional limitations of extrapolating animal data to human disease. However, there are clearly methodological challenges and limitations in studying cerebral autoregulation in clinical AD, as discussed above, that prevent us from definitely concluding that the autoregulatory properties of the cerebrovascular bed are preserved in AD. Further efforts are needed before we can come to truly understand the complex interaction between AD and cerebrovascular disease.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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