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Authors

Grinberg, Lea Tenenholz

Korczyn, Amos D

Heinsen, Helmut

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Cerebral amyloid angiopathy impact on endothelium

Lea Tenenholz Grinberg^{a,b}, Amos D. Korczyn^c, and Helmut Heinsen^d

^aDepartment of Neurology, University of California San Francisco, 305 Parnassus Avenue, San Francisco, CA, 94143, USA

^bAging Brain Study Group, LIM-22, Department of Pathology, University of Sao Paulo Medical School. Av Dr Arnaldo, 455 sala 1353. CEP 01246903, Sao Paulo – SP, Brazil

^cSackler School of Medicine, : Department of Neurology, Tel-Aviv University, Ramat Aviv 69978, Israel

^dLaboratory of Morphological Brain Research, Psychiatrics Clinics, University of Wuerzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany

Abstract

Cerebral amyloid angiopathy (CAA) is an age-associated disease characterized by amyloid deposition in cerebral and meningeal vessel walls. CAA is detected in the majority of the individuals with dementia and also in a large number of non-demented elderly individuals. In addition, CAA is strongly associated with Alzheimer's disease (AD) pathology. Mechanical consequences including intra-cerebral or subarachnoid hemorrhage remains CAA most feared complication, but only a small fraction of CAA results in severe bleeding. On the hand the non-mechanical consequences in cerebrovascular regulation are prevalent and may be even more deleterious. Studies of animal models have provided strong evidence linking the vasoactive A β 1–40, the main species found in CAA, to disturbances in endothelial-dependent factors, disrupting cerebrovascular regulation. Here, we aimed to review experimental findings regarding the non-mechanical consequences of CAA for cerebrovascular regulation and discuss the implications of these results to clinical practice.

Keywords

amyloid; angiopathy; dementia; Alzheimer's disease; animal models; endothelium; cerebrovascular dysfunction; blood brain barrier

Introduction

Approximately 20% of the left ventricular cardiac output is directed to the brain, even though it only represents about 2% of the total body mass. This clearly illustrates that brain function depends on the continuous and highly-regulated delivery of blood to meet energy requirements and to clear deleterious metabolic by-products. Even short periods of cerebrovascular impairment can lead to neuronal damage by compromising the steady

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Corresponding author: Helmut Heinsen, Laboratory of Morphological Brain Research, Psychiatrics Clinics, University of Wuerzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany, heinsen@mail.uni-wuerzburg.de, Phone: + 49 972 201775051.

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supply of essential metabolites such as oxygen, amino acids and glucose (Bell and Zlokovic, 2009; Kalaria, 2009). This is demonstrated by the dramatic and irreversible neurological deficits caused by even a quickly reversed thromboembolism. The brain vascular system is regulated independently of the systemic circulation (van Beek et al., 2008). This auto-regulatory ability delays cerebral ischemia during low blood pressure states, and diminishes the risk of blood–brain barrier (BBB) disruption and brain edema during systemic hypertensive episodes. Ischemic and hemorrhagic lesions resulting from large brain vessel disease and their consequences are easily detected, even by low resolution imaging or simple gross inspection during autopsy (Yoshiura et al., 1999). On the other hand, identification of small vessel (arterioles, capillaries and venules) changes often requires special histological processing and comprehensive, meticulous microscopic investigation. Small vessels comprise less than 10% of the total brain volume, but are of paramount importance in regulating cerebral blood flow, oxygen supply, and metabolite exchange.

Cerebral amyloid angiopathy (CAA) is an age-associated disease characterized by amyloid deposition in vessel walls of meningeal arteries and capillaries, as well as intra-cortical vessels. Experimental evidence suggests that the non-mechanical consequences of CAA are even more deleterious than the classically acknowledged mechanical consequences of this disease, which include lethal cerebral hemorrhage. Here, we aimed to review experimental findings regarding the non-mechanical consequences of CAA for cerebrovascular regulation and discuss the implications of these results to clinical practice.

Epidemiology and neuropathological characteristics of CAA

CAA neuropathology was described over a century ago, and the condition received its current nomenclature several decades later (Biffi and Greenberg, 2011; Fischer, 1910; Oppenheim, 1909). However, it only gained importance and became the subject of systematic investigation when its association with lethal cerebral hemorrhage was identified (Jellinger, 1977; Okazaki et al., 1979). Current evidence indicates that CAA is much more prevalent than hitherto appreciated, detected in one third of non-demented elderly individuals and two thirds of elderly individuals with dementia in population-based clinicopathological studies (Charidimou et al., 2012). CAA is strongly associated with Alzheimer's disease (AD) pathology, although it is not clear what impact CAA has on cognitive decline in these cases (Jellinger, 2002; Thal et al., 2003).

CAA is characterized by deposition of amyloid formed mainly from beta-amyloid peptides (A β) in the walls of leptomeningeal and parenchymal vessels' (Jellinger, 2002). A β is a product of amyloid precursor protein proteolytic cleavage by β -secretase and γ -secretase. The resulting peptides predominantly have 40 (A β 1-40) or 42 (A β 1-42) amino acid residues. A β may polymerize into the insoluble fibrils found in AD plaques, mainly composed of A β 1-42, and in the deposits found in vessel walls in CAA, mainly composed of A β 1-40. In CAA, immunohistochemical and electron microscopic investigations show A β fibrils first deposited in the abluminal aspect of the basal lamina around smooth muscle cells, followed by a gradual spreading towards the internal elastic lamina of arteries and the endothelium of arterioles. The smooth muscle cells degenerate as the disease progresses (Wisniewski et al., 1994). In capillaries, which are devoid of smooth muscle, A β fibrils are found within the basal lamina and adjacent neuropil. Endothelial cells are apparently well preserved, even in severe CAA (Pezzini et al., 2009).

Some of the open questions related to CAA concern the origin or source of the amyloid deposited in the vessel walls (Smith and Greenberg, 2009) and the reason for its predilection for occipital, parietal and frontal cortices, whereas the deep central gray nuclei, white matter and brainstem are rarely affected (Pezzini et al., 2009; Vinters, 1987).

CAA complications

CAA complications can occur depending on the extent and location of disease pathology. Intra-cerebral or subarachnoid hemorrhage remains CAA most feared complication, caused by A β accumulation in the leptomeningeal and intracranial arteries, with smooth muscle loss and adventitial involvement, leading to aneurysm formation, fibrinoid necrosis, and rupture. However, the proportionally low number of CAA-associated hemorrhages suggests that only a small fraction of CAA cases result in severe bleeding (Jellinger et al., 2007). This does not mean, however, that CAA is benign. For instance, in capillaries, amyloid accumulation leads to wall brittleness and lumen obstruction, causes of small ischemic lesions and microbleeds (Thal et al., 2009), which are emerging as potential contributors to cognitive decline (De Reuck et al., 2011; Nakata-Kudo et al., 2006).

In addition, non-mechanical changes in cerebrovascular regulation are emerging as important CAA complications. Several independent studies of animal models have provided strong evidence linking the vasoactive A β 1–40 to disturbances in endothelial-dependent factors, disrupting cerebrovascular regulation (Bamberger et al., 2003; Niwa et al., 2000) (Farkas and Luiten, 2001; Frackowiak et al., 1994).

A β and cerebrovascular dysregulation

Decreased cerebral blood flow negatively affects brain metabolism and synthesis of proteins required for memory and learning (Bell and Zlokovic, 2009). Cerebral flow dysregulation is an early feature of AD. The mechanisms causing such dysregulation are poorly understood, but some evidence suggests A β as an important culprit. The first clues suggesting that A β altered cerebral autoregulation came from neuroimaging studies in the early stages of AD and in asymptomatic, but genetically predisposed individuals (Iadecola, 2003; Paris et al., 2003). On the experimental side, several investigations using transgenic animals or human cell lines established that both soluble and insoluble forms of A β , in particular the CAA-associated A β 1–40, were strongly vasoactive.

Attempts to understand the mechanisms mediating A β -associated vascular dysregulation using isolated cerebral arteries suggested that brain parenchyma participation was not required, indicating a direct effect of A β on the vessels (Crawford et al., 1998; Niwa et al., 2001; Thomas et al., 1996). To investigate A β effects on cerebrovascular regulation further, transgenic mice Tg2576 overexpressing a mutated form of human APP, which show age-dependent elevations in brain A β and behavioral deficits (Hsiao et al., 1996), have been extensively studied. This APP mutation leads to the development of CAA in older mice, who also show severe vasodilatory dysfunction compared to young Tg2576 free of CAA (Christie et al., 2001). These mice start showing progressive cerebrovascular dysfunction when the levels of soluble A β rise, in a dose-dependent fashion which is independent of the presence of A β deposits (Niwa et al., 2000; Zhang et al., 1997). Further observations established endothelium-dependent pathways as important targets of A β -mediated vascular toxicity (Price et al., 2004). A series of elegant experiments comparing APP and wild-type mice showed that intrathecal injection of A β 1–40 altered the response of the cerebral vessels to several endothelium-dependent vasodilators, while no effect was seen on the response to endothelium-independent vasodilators (Iadecola et al., 1999). Indeed, application of exogenous A β caused endothelium-dependent vasoconstriction in normal blood vessels *ex vivo* (Thomas et al., 1996; Townsend et al., 2002). Since cerebral endothelial cells remain ultrastructurally intact in APP mice and in human CAA, these authors suggested that changes in a common pathway utilized by endothelium-dependent vasodilators, rather than endothelium structural problems, are the cause of this dysfunction. Impaired endothelium-dependent vasodilatation is found in many cardiovascular conditions,

such as atherosclerosis, hypertension, heart failure and diabetes mellitus (Cai and Harrison, 2000). In the presence of A β 1-40, dysfunction of endothelium-dependent vasodilatation is often mediated by pathways involving production of reactive oxygen species (ROS) mediated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Iadecola, 2003), a multi-unit enzyme that requires p67phox, p47phox, p40phox and GTPase Rac for activation (Ray and Shah, 2005). One of its main functions is to catalyze the production of superoxide from oxygen (Babior, 2004), by coupling the latter to electrons transferred from intracellular NADPH. NADPH oxidase activation occurs through multiple mechanisms, such as angiotensin II (Li and Shah, 2003), growth factors (Ushio-Fukai et al., 2002), cytokines (Frey et al., 2002) and reduced bioavailability of nitric oxide (Park et al., 2011). CD36 is an endothelial membrane glycoprotein acting as a scavenger receptor. A β -induced ROS production through a signaling pathway culminating in Rac activation is mediated by a molecular complex that includes CD36 (Coraci et al., 2002). In experimental studies using CD36-null mice or APP mice lacking CD36, A β 1-40 did not cause endothelial dysfunction, regardless of the brain A β levels (Park et al., 2011). In addition, the use of CD36 blocking antibodies reversed endothelial dysfunction in APP mice (Park et al., 2011). These results suggest that CD36 inactivation is vasoprotective against A β toxicity, and its suppression could potentially ameliorate A β -mediated cerebrovascular dysfunction in humans.

Besides impaired vasodilatation, other A β -mediated endothelial effects have been proposed. Permeability of the BBB is controlled by endothelial cells, which are kept together by tight junction (TJ) proteins. BBB defects are associated with reduced cognition in AD (Zlokovic, 2008). Experimental studies show a detrimental effect of A β on some TJ proteins, with increased BBB permeability. In rat endothelial cells treated with A β 1-42, TJ transmembrane proteins claudin-5 and ZO-2 are mislocalized to the cytoplasm (Marco and Skaper, 2006). Human brain endothelial cell lines exposed to A β 1-40 showed increased permeability associated with a decrease of occludin levels and no changes in claudin-5 and ZO-1 levels (Tai et al., 2010). On the other hand, another study found A β -induced changes in claudin levels (Hartz et al., 2012). Therefore, although TJ proteins are probably involved in A β -induced cerebrovascular dysfunction, the mechanisms are not yet clear.

CAA-affected capillaries demonstrate loss of TJ proteins associated with a pericapillary increase in activated microglia expressing NADPH oxidase-2 (Carrano et al., 2011).

Several agents have been shown to ameliorate A β -mediated vascular dysfunction *in vitro*. A β 1-42 dose-dependent generation of ROS was halted by the administration of antioxidants, NOX-2 inhibitors, and by blocking receptors for advanced glycation end-products (RAGE) in human brain endothelial cell lines (Carrano et al., 2011). TJ protein changes were ameliorated by inhibition of c-Jun N-terminal kinases (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) pathways, suggesting that these could represent potential therapeutic targets (Tai et al., 2010; Vukic et al., 2009).

A β -mediated cerebrovascular dysfunction in humans

The findings of the experimental studies reported above cannot yet be confirmed in humans, using currently available methods. However, several indirect observations indicate that increased A β levels are also detrimental to human cerebrovascular regulation, and population-based studies found an association between CAA and cognitive decline (2001; Pfeifer et al., 2002).

Imaging studies have shown that resting cerebral blood flow is reduced in selected neocortical regions in AD (Jagust et al., 1997; Johnson et al., 1998; Prohovnik, 1998). This effect could be partially mediated by vascular dysfunction. Doppler ultrasound studies found that CAA was associated with decreased vascular reactivity in response to visual stimulation

(Smith et al., 2008). Another study using functional MRI identified robust differences in both amplitude and timing of the response to visual stimulation in advanced CAA (Dumas et al., 2012). On the other hand, some CAA-associated effects found in mouse models, such as changes in evoked response to CO₂ measured in the middle cerebral artery (Shin et al., 2007), could not be reproduced consistently in humans (Bar et al., 2007; Jagust et al., 1997; Yamaguchi et al., 1980). It is yet to be determined if these findings reflect true differences between CAA pathogenesis in humans and rodents, or if they are due to the occipital lobe predilection in humans, which makes the middle cerebral artery a poor target for such investigations. Finally, a lack of power in the statistical analyses has to be considered as a limitation of the human studies.

NADPH oxidase was implicated in A β -mediated vascular dysfunction in experimental models (Iadecola, 2003) and this enzyme is up-regulated in AD (Shimohama et al., 2000).

CAA was also associated with ischemic lesions, especially in small vessels (Haglund et al., 2006; Olichney et al., 2000; Suter et al., 2002). This observation is corroborated by animal models, where increased A β levels increase brain vulnerability to ischemic damage via disturbances in endothelium-dependent vascular reactivity (Zhang et al., 1997). In turn, ischemic brain lesions induced in an APP^{swe:PS1dE9} mouse model (Jankowsky et al., 2001) were associated with increased A β deposition (Garcia-Alloza et al., 2011), suggesting a bi-directional relationship between A β and ischemia. Such a relationship would perpetuate the detrimental effects of both phenomena.

Further studies are needed to show if A β -induced vascular dysfunction is as deleterious in humans as it is in experimental models, and if the pathways involved are similar. If similarities are detected, substances proven to ameliorate this damage in experimental models are already in use for other human conditions such as Vitamin E (Venugopal et al., 2004) or SS31 peptide (Cho et al., 2007) for inhibiting CD36, and apocynin, a NADPH oxidase inhibitor (Lull et al., 2011). These could therefore be prioritized as potential therapeutic agents targeting vascular dysfunction in AD clinical trials.

Conclusions

In this paper, we aimed to highlight soluble and insoluble A β -mediated cerebrovascular dysfunction, mediated via endothelial pathways. Although direct observations were made using animal models, the results are robust enough to suggest that the same effects may occur in humans. If human brain endothelial cells are prone to the same harmful effects of A β 1–40 as are seen in experimental models, dysfunctional cerebrovascular regulation and BBB deficits would be much more important than mechanical CAA complications and would explain part of the cognitive decline observed in individuals with CAA.

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Highlights

- Cerebral amyloid angiopathy (CAA) is an age-associated disease characterized by amyloid deposition in cerebral and meningeal vessel walls
- CAA causes mechanical and non-mechanical complications
- The non-mechanical deleterious consequences in cerebrovascular regulation are prevalent
- Studies of animal models have linked the vasoactive A β 1–40, the main species found in CAA, to disturbances in endothelial-dependent factors, disrupting cerebrovascular regulation
- If human brain endothelial cells are prone to the same harmful effects of A β 1–40 as are seen in experimental models, dysfunctional cerebrovascular regulation and BBB deficits would be much more important than mechanical CAA complications and would explain part of the cognitive decline observed in individuals with CAA



Figure 1. (A) Formalin fixed brain slice of a 60 years old male with two focus of cerebral hemorrhage (arrows). (B) Histological examination showed A β deposition in form of plaques and in vessels (arrow)(immunohistochemistry for A β – scale bar:100 μ m). In this case, the bleeding was probably a CAA complication