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Are Alzheimer’s disease, hypertension, and cerebrocapillary damage related?☆

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Abstract

Alzheimer’s disease (AD) patients are often subject to vascular dysfunction besides their specific CNS pathology, which warrants further examination of the interaction between vascular factors and the development of dementia. The association of decreased cerebral blood flow (CBF) or hypertension with AD has been a target of growing interest. Parallel with physiological changes, the cerebral capillaries in AD are also prone to degenerative processes. The microvascular abnormalities that are the result of such degeneration may be the morphological correlates of the vascular pathophysiology pointing to a compromised nutrient transport through the capillaries. Animal models have been developed to study the consequences of hypertension and reduced CBF. Spontaneously hypertensive rats are widely used in hypertension research whereas ligation of the carotid arteries has become a method to produce cerebral hypoperfusion. Based on these models, we propose a relationship between hypertension, cerebral hypoperfusion, cerebral capillary malformation and cognitive decline as it occurs in AD. We suggest that the above conditions are functionally related and can contribute to the progression of AD. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Alzheimer’s disease; Chronic hypertension; Cerebral hypoperfusion; Carotid occlusion; Cerebral capillaries

1. Hypertension in Alzheimer’s disease

Vascular factors, which may contribute to the development of dementia, have gained growing attention in recent years [10,55]. Particularly hypertension, being a frequently occurring condition with advancing age has come into focus for its major role in the development of stroke and its association with atherosclerosis. Clinical studies were aimed at clarifying a presumed relationship between chronic hypertension and the onset of dementia because an elevated blood pressure was thought to interfere with proper cerebral circulation and neuronal metabolism. This idea found compelling support in the observation that vascular dementia (VD) consistently coincided with high blood pressure [18, 23,26,33]. The role of hypertension in the pathogenesis of Alzheimer’s disease (AD), another prominent type of dementia appeared to be more complicated to elucidate. Several epidemiological studies investigated the interaction of elevated blood pressure and AD but a final agreement about a causal relationship has not been reached, yet. Nevertheless, based on several studies [32,14,48] a hypothesis was proposed that the blood pressure of AD patients probably varies according to the stage of the disease and that hypertension characteristically precedes the diagnosis of cognitive impairment with at least 10 years [49]. According to this theory, patients suffering from chronic hypertension during their midlife have a higher chance for developing AD at older age. The theory proposed by Skoog [49] was further underscored by the detection of an increased amount of senile plaques and neurofibrillary tangles in the brains of hypertensive individuals [50]. Thus, chronically high blood pressure can be considered as a condition, which increases the potential to develop dementia. Such tendency was also

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indirectly shown by the preventive effect of anti-hypertensive drugs on the incidence of AD [19].

In line with the hypothesis that hypertension can act as a risk factor for AD, in vitro and in vivo experiments were designed to investigate the effect of circulating β-amyloid - the peptide typically accumulating in AD brains—on blood pressure. Isolated aorta preparations and in vivo β-amyloid infusion demonstrated the vasoconstrictive effect of β-amyloid [1,52].

2. Hypertension, dementia, and CBF

Patients suffering from chronic hypertension can often display signs of additional vascular abnormalities. For example, high blood pressure is generally accompanied by arteriosclerosis or deformations of larger peripheral vessels exerting additional harmful effects on the circulation. The rigid vessel walls and the considerably narrowed lumen diameter further hinder the maintenance of a normal blood pressure by increasing peripheral resistance. Besides such systemic damage, abnormally high pressure can also threaten an optimal cerebral blood supply, as it was show in hypertensive individuals. When the CBF of hypertensive patients was measured with PET or the 133Xe-inhalation method, and the data compared to those of normotensive individuals, reduced flow rate was recorded in the hypertensive patients [21,37,39]. In addition, the drop in CBF was less pronounced in high blood pressure patients who were receiving an anti-hypertensive treatment [39].

Animal studies lead to similar observations: the CBF of spontaneously hypertensive (SHR) rats appeared to be reduced, as well, where the compromised cerebral circulation was already detectable at 4 months of age [22,31]. This latter finding suggests that an accelerating age effect in a hypertension-induced drop in CBF is not crucial; instead, hypertension itself can already create an unfavorable cerebral circulation. Nevertheless, the enhanced breakdown of cerebral circulation at older age should not be neglected considering that even lower CBF values were measured in aged hypertensive animals [31]. Further indication of a decreased CBF can be an elevated lactate concentration in the jugular venous blood, which indicates cerebral anaerobic glycolisis. An increased jugular lactate concentration was also described in hypoperfused SHR rats [12]. A conceivable explanation of reduced CBF in hypertension may be that a typical atherosclerosis of the carotid arteries contributes to the development of insufficient cerebral blood supply. Another interpretation may argue for a damaged cerebrovascular autoregulation. Dickinson [12] however discussed a preserved cerebrovascular autoregulatory capacity of the brain and suggested an alternative deficient vascular process. According to this view, the cyclic opening and shutting of cerebral capillaries normally cares for a regular oscillation in the cerebral arteriolar calibre, which process seems to be compromised in the SHR animals. Whatever the underlying mechanism may be, a reduced CBF seems to consistently accompany chronic hypertension.

A defective brain circulation has also become a target of increasing interest in the pathophysiology of AD. Clinical measurements of regional CBF by the noninvasive SPECT method have indicated that AD is accompanied by a decreased regional CBF in the hippocampal formation, the temporal cortex, the parietal cortex and the frontal cortex [4,11,13,29,36,40,41,46,53]. The region specificity is remarkable because the typical neuropathological hallmarks of AD also appear first and most extensively in the entorhinal region and the temporal cortex. Based on these observations, it would still remain uncertain whether a reduced CBF in AD is caused by a possible loss of cerebrovascular autoregulation due to the disease-specific decaying of neuronal integrity or whether the low CBF is a contributing factor to the development of dementia symptoms. The latter possibility appears to be more probable considering the neurological complications arising shortly after a cardiac surgery. Case reports and reviews about the neural effects of such a serious surgical intervention reported that the brain can suffer hypoperfusion during the surgical procedure after which recovering patients often have postoperative cognitive disorders [24,25,51]. A plausible explanation of the phenomenon is that the decreased, intraoperative cerebral perfusion can create an imbalance between oxygen demand and supply in the brain, which is probably responsible for the postoperative memory deficit after cardiac surgery [5]. Further evidence supporting the view that reduced CBF can precede neuronal degeneration in dementia, would be an increased oxygen extraction accompanying the decreased CBF in AD. Pantoni and Garcia [43] noted that lowered CBF was considered secondary to dementia-related cerebral atrophy in case an increase in oxygen extraction would not couple the drop in CBF. However, recent reports suggested that oxygen extraction in AD brains increased whereas CBF reduced [36,53]. These findings support the hypothesis that compromised cerebral perfusion arises before neuronal disintegration in dementia.

In summary, a reduced CBF has been reported concurrent with chronic hypertension both in humans and in experimental animals. Furthermore, the involvement of a decreased CBF in AD has also been shown. Such similarity in the alteration of cerebral circulation in the two pathological conditions, namely chronic hypertension and AD, may imply an analogous chain of cerebrovascular and neural events in the two conditions. Below, we intend to offer an explanation of such a possible sequence of cerebral processes triggered by an insufficient brain perfusion.

3. Reduced CBF and cerebral capillary ultrastructure

Separate studies have investigated cerebrovascular physiological parameters and their structural correlates in patient
groups of AD. The clinical line of research presented measurements of CBF with non-invasive scanning methods whereas pathology-oriented research groups analyzed vascular integrity and described morphological alterations of cerebral vessels in AD.

Sufficient blood supply to the brain can be of critical importance in taking care of a proper nutrient delivery and meeting the metabolic demands of an optimal cognitive performance. A decreased CBF can impose a chronically reduced availability of glucose and oxygen to the brain leading to suboptimal neuronal metabolism. Such energy crisis is reflected in the findings that the cerebral metabolic rate for oxygen and glucose, as well as the density of glucose transporter sites in the cerebral capillary walls were distinctly reduced in AD [20,27,28,30,35]. The deprivation of neural tissue of the essential nutrients can derive from either the lower flow rate itself - implying a reduced volume of blood reaching the cerebral vasculature— or the affected permeability of the capillary walls due to structural anomalies [8]. Most probably, the two factors are mutually and progressively related, and a chronically low CBF together with the abnormal vascular morphology can jeopardize sufficient nutrient trafficking in the brain.

The cerebrovascular structural lesions that can appear in AD were shown by a number of research groups. Bueé et al. [2] described abnormally twisted, tortuous fragmented vessels or glomerular vascular loop formations in a light microscopic study whereas Claudio [3] reported ultrastructural capillary pathology in biopsy tissue from AD brains at the electron microscopic level. Others reported similar capillary deformities found in post mortem AD material [30,47]. Our own studies also gathered evidence that the cerebrocortical capillaries of AD and other dementing patients suffer considerable pathological changes [15,16]. Electron microscopic analysis of post mortem samples from the cingulate cortex demonstrated that the capillary basement membrane was a preferential site of ultrastructural degradation in AD and Parkinson’s disease with dementia (PDd). The local thickening and distortion of the basement membrane, and extracellular deposits in the vessel walls (that often contained collagen) appeared to be a prominent degenerative feature whereas the condition of pericytes was not affected. The local thickening of the basement membrane means unusually enlarged basement membrane segments where the thickness of the membrane is at least twice of the intact parts of the same vessel. Additional collagen fiber deposits can be also frequently encountered in the capillary basement membrane of affected microvessels. Such capillaries with basement membrane deposits occurred two times more frequently in AD and PDd brains than in control cases in our study (Fig. 1A) indicating a dementia-related damage. This interpretation was supported by a correlation analysis between capillary degeneration and age of the patients in our study, where no significant correspondence was found [16].

The decreased CBF and a compromised cerebral capillary ultrastructure in AD curiously coincide but their proposed functional and causal interaction remains to be demonstrated. Animal models offer a good possibility to reveal the potential underlying mechanisms that link reduced CBF and the decaying capillary condition in the brain. For example, the permanent ligation of both common carotid arteries of rats (two vessel occlusion, 2VO) was developed as a model of chronic cerebral hypoperfusion, where the blood supply to the brain is reduced to about 70% of the original...
rate [54]. This agrees with the drop in CBF in the hippocampus and temporal cortex of AD patients [13,41]. We have shown recently that 2VO causes structural abnormalities of cerebral capillaries reminiscent of those seen in AD. Such microvascular lesions in the rat include region-specific local thickening of the basement membrane and microvascular collagen accumulation in the hippocampal formation after 14 months of cerebral hypoperfusion [6]. Our results showed that the incidence of capillaries with basement membrane pathology increased from a 30% control value found in sham operated animals to more than 50% in the 2VO group (Fig. 1B). Thus, the experiment suggests a functional link between chronically reduced CBF and cerebral capillary damage, with cerebral hypoperfusion being the likely trigger for the formation of the ultrastructural vascular deformities.

It is interesting to note that we have also encountered microvascular lesions in the frontal cortex of spontaneously hypertensive stroke prone rats (SHR-SP) [17] (Fig. 2.). Like in the 2VO model, the ratio of affected vessels increased from 30% of normotensive controls to 50% in the SHR-SP strain at the age of 60 weeks (Fig. 1B). Besides, others had shown that the hypertensive animals had a reduced CBF [22,31]. These findings provide additional evidence for causal interaction between chronically low CBF and microvascular degeneration, in this case, under hypertensive conditions.

4. Cerebral capillary ultrastructure and cognitive impairment

The AD patients in our study showing the above described typical capillary aberrations had been diagnosed as probable or definite cases with respect to the CERAD scale and they were in phase IV or V of the disease according to

Fig. 2. Electron microscopic computer generated images of ultrastructural cerebral capillary lesions in experimental cerebral hypoperfusion (2VO) (A, B, C) and chronic hypertension in spontaneously hypertensive stroke prone rats (SHR-SP) (D, E, F). A and D: local thickening of the basement membrane in 2VO (A) and SHR-SP (D). B and E: amorphous, fibrous deposits in the basement membrane in 2VO (B) and SHR-SP (E). C and F: fibrosis in the capillary basement membrane in 2VO (C) and SHR-SP (F). Abbreviations: *: capillary basement membrane, e: endothelial cell, l: microvascular lumen, p: pericytic cytoplasm.
the Braak scoring system (Table 1) [16]. The dementing Parkinson’s disease cases were displaying similar neuropathology (Table 1). Such neuropathological classification implicates serious cognitive impairment, which coincided with the typical vascular pathology (local thickening of the microvessel walls) that we observed. The exact contribution of capillary basement membrane degeneration in the development of cognitive dysfunction in AD is hard to specify based on post mortem analysis alone but the 2VO experiments may offer some guidelines. 2VO animals were repeatedly tested in spatial learning paradigms such as the Morris water maze and the eight arm radial maze to establish their learning and memory capacity. Carotid occlusion was performed either on young or on old animals [6,7,38, 42] and behavioral testing after permanent vessel occlusion was performed at various time points depending on the experimental paradigm. The post-operative period between surgery and testing varied in different studies from 2 weeks...
Despite all these variables, the experimental cerebral hypoperfusion consistently lead to a subtle but significant learning impairment in all these cases. In addition, the poorer spatial memory of the 2VO rats was reflected in a deteriorating neuronal integrity. After 180 days of permanent 2VO, apoptotic neuronal cell death and an increased glial GFAP expression took place in the hippocampal CA1 region [44,45].

Our own 2VO studies focused more specifically on the alteration of capillary integrity in the hippocampal region. The capillary basement membrane displayed local thickening and collagen deposits considerably more frequently in the 2VO animals than in sham operated controls as an apparent result of chronic cerebral hypoperfusion. We furthermore established a correlation between the percentage of capillaries with ultrastructural pathology in the hippocampus and the water maze performance of the animals at 14 months after the induction of 2VO (Fig. 3). The distance the animals traveled to find the hidden platform in the maze was taken as a marker of their learning capacity. We found a highly significant correlation in the hippocampal CA1 region between deteriorating cerebral microvascular condition and declining spatial learning skills indicated by the increased length of the animals’ swim paths [6]. Thus, the 2VO-induced chronic cerebral hypoperfusion showed an overt tendency to hamper spatial learning, which paralleled capillary damage in the hippocampus.

Independent of the 2VO experiments, SHR-SP animals were also tested in the Morris water maze and radial arm maze for their learning skills [6,7,38,42,44,56]. The Morris water maze test detects hippocampus-dependent spatial learning skills and reference memory whereas the radial arm maze is designed to test both reference and short-term working memory. Comparison of the performance of normotensive and hypertensive (SHR-SP) animals in these experimental paradigms clearly demonstrated the effect of hypertension on brain function. The learning tests of SHR-SP rats lead to results, which corresponded with the findings in the cerebral hypoperfusion experiments (2VO). Both the 2VO animals and the SHR-SP rats performed significantly worse than their controls in the Morris water maze or the eight arm radial maze. The 2VO animals and the SHR-SP rats swam a longer distance than their controls before locating the hidden platform in the water maze and committed more errors in the radial maze by entering arms that they had already visited. Such observations are con-

[42,44] to 14 months [6]. Despite all these variables, the experimental cerebral hypoperfusion consistently lead to a subtle but significant learning impairment in all these cases. In addition, the poorer spatial memory of the 2VO rats was reflected in a deteriorating neuronal integrity. After 180 days of permanent 2VO, apoptotic neuronal cell death and an increased glial GFAP expression took place in the hippocampal CA1 region [44,45].

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vincing evidence for a suboptimal learning and memory capacity in chronic hypertension.

Moreover, our experiments showed that 40-week old SHR-SP rats performed significantly worse than their Wistar–Kyoto controls in the hippocampus-dependent holeboard spatial learning test [34]. The compromised learning capacity of the hypertensive group was also consistently reflected in learning task-elicited neuronal biochemical parameters in the hippocampal CA1 area. Specifically, PKCγ immunoreactivity, which is normally enhanced by the learning process and is a sign of neuronal activation, was found less pronounced in SHR-SP animals compared to controls. These findings provide further support for a meager cerebral functioning, which accompanies a persistently high blood pressure.

Besides recording spatial learning abilities, we also assessed a more general behavioral profile of the SHR-SP animals compared to a normotensive age-matched control group in a novelty-induced behavioral arousal paradigm. The rats were observed for 60 min in a small open field and their behavioral activity was recorded. Such a novelty-induced activity test can help to estimate the exploratory arousal of the animals. The analysis of the collected data showed that rearing and grooming behavior occurred significantly less frequently in the SHR-SP group than in the control animals (Fig. 4) which is regarded indicative for a suppressed behavioral activity. Because a decaying exploration normally occurs with aging, the lower arousal level of the SHR-SP rats noted here may refer to an accelerated aging process that results from chronic hypertension. To know the scale of the actually prevailing hypertension in the experimental animals, we also recorded the systolic blood pressure with the tail cuff method under mild ether anesthesia. The average value for the SHR-SP group was 180 mmHg whereas the blood pressure in normotensive controls reached an average of 110 mmHg. When we correlated the blood pressure values with the percentage of intact capillaries, we found a strong relationship (Fig. 5A). The decreasing incidence of intact microvessels significantly corresponded to the increasing systolic pressure. In addition, a positive correlation was established between the rearing scores and the percentage of healthy cerebral capillaries in the frontal cortex indicating a higher behavioral activity coinciding with a higher incidence of intact cerebral capillaries (Fig. 5B). These findings show that the decaying condition of cerebral microvessels in hypertension can indeed compromise the optimal operation of neuronal networks and the consequent behavioral characteristics.

The above presented 2VO experiments and the SHR-SP studies of chronic hypertension both presented an example for the coincidence of cerebral capillary malformations and memory deficit. We hypothesize that these two degenerative properties stand in an interactive correspondence. The structural aberrations of the capillaries penetrating the neural tissue probably hamper nutrient trafficking to the neuronal cells, thus compromising an adequate energy production required for optimal neuronal operation. This suggestion finds support in the recognition that cytochrome oxidase activity—the terminal enzyme of the mitochondrial electron transport chain—in the hippocampus and posterior parietal cortex of 2VO rats is remarkably decreased [9]. A lower cytochrome oxidase activity can imply a consequent impairment in ATP synthesis, which may finally become manifest in cognitive deficits.

5. Conclusion

The present overview has been attempting to elucidate the nature and consequences of the causal role of hypertension in the development of cognitive impairment in AD. We presented relevant animal models, such as the sponta-
ously hypertensive rat strain (SHR-SP) and permanent occlusion of the common carotid arteries (2VO) to support and clarify the findings of human studies on hypertension and AD. Because our experimental work focused on the causal factors leading to cerebral microvascular lesions and associated cognitive decline, we have emphasized the importance of cerebrocirculatory deficiencies in the pathophysiology of dementia.

Both animal models, namely SHR-SP and 2VO, verified the observation of a reduced CBF detected in chronic hypertension and AD in humans. Considering such a remarkably coinciding similarity shared by the two conditions (hypertension and AD) and the reported prevalence of hypertension in dementia, a decreased CBF can be regarded as a consequence of a chronically high blood pressure. The lowered CBF can, in turn, give rise to a chain of pathological events in the brain. As shown by 2VO, a suboptimal cerebral perfusion can generate typical ultrastructural damage of cerebral capillary walls. Such characteristic morphological degeneration of microvessels in the brain can be implicated in a hampered nutrient delivery to the neuropil and a consequent neuronal metabolic crisis. A convincing confirmation for this claim can be a decreased cytochrome oxidase activity observed in 2VO animals. Finally, the inadequate availability of energy substrates to the neural tissue can become manifest in a mild but characteristic memory deficit with its neuropathological correlates (for example: decreased PKC\(\gamma\) activity, increased astrocytic proliferation or apoptotic cell death). The above described chain of events followed in experimental animals may correspond with individual observations in AD, such as a reduced CBF, cerebrocortical capillary lesions, a decreased metabolic rate for glucose and oxygen in the brain, degenerating neuronal integrity and a cognitive impairment. We suggest that a prevailing hypertensive condition may be identified as an initial trigger that can lead to such a sequence of cerebral events finally contributing to the progression of AD.

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