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Cholinergically mediated augmentation of cerebral perfusion in Alzheimer's disease and related cognitive disorders: The Cholinergic–Vascular Hypothesis

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Abstract
The treatment of Alzheimer’s disease (AD) with cholinesterase inhibitors (ChEIs) is based on the cholinergic hypothesis. This hypothesis fails to account for the global nature of the clinical effects of ChEIs, for the replication of these effects in other dementias, and for the strong and unpredictable intraindividual variation in response to treatment. These findings may be better explained by the premise that ChEIs primarily act by augmenting cerebral perfusion: the cholinergic–vascular hypothesis. This article will review the evidence from preclinical and clinical investigations on the vascular role of the cholinergic neural system. The clinical relevance of this hypothesis is discussed with respect to its interactions with the vascular and amyloid hypotheses of AD. Implications for treatment are indicated. Finally, we propose that the role of the cholinergic system in neurovascular regulation and functional hyperemia elucidates how the cholinergic deficit in AD contributes to the clinical and pathological features of this disease.
The treatment of Alzheimer’s disease (AD) with cholinesterase inhibitors (ChEIs) is based on the cholinergic hypothesis\(^1\text{-}\(^3\). Thirty years ago, post mortem studies revealed a severe loss of cholinergic innervation in brains of AD patients\(^1\text{-}\(^2\). The severity of this cholinergic deficit was later found to correlate with the level of cognitive impairment\(^4\text{-}\(^5\). Furthermore, it was observed that the loss of cholinergic innervation in AD occurs most prominently in the hippocampus and temporal cortex; this loss could account for the clinical presentation with a predominant and severe loss of memory\(^6\text{-}\(^7\). Although the concept of a cholinergic deficit as a monocausal model for AD has long since been abandoned, there is solid evidence for the important role of the cholinergic system in the processes of memory, attention, and behavior\(^6\text{-}\(^8\).

ChEIs (donepezil, galantamine, and rivastigmine) reduce the synaptic breakdown of acetylcholine (Ach) and thus partially correct the cholinergic deficit. Early expectations were that these drugs would produce a significant improvement in memory. In practice, however, treatment effects are far more global and consist of modest improvements in cognition, attention, executive function (including activities of daily living), and global rating scales\(^9\text{-}\(^11\). In addition, the response to treatment varies markedly among patients, and it is currently unpredictable whether an individual patient will benefit from therapy. These findings cannot be fully explained from the cholinergic hypothesis.

Moreover, the observed treatment effects are not specific for AD. Very similar outcomes can be found in patients with vascular cognitive impairment, dementia with Parkinson’s disease, and dementia with Lewy bodies\(^12\text{-}\(^15\). It should be noted that this nonspecificity of treatment effects may in part reflect the current lack of precision in diagnosing and separating “pure” forms of AD and other dementias. In contrast, these data could point toward a different mode of action of ChEIs than is suggested by the cholinergic hypothesis. A further argument for this explanation is the finding that healthy individuals receiving ChEIs show increased attention and reaction speed and, in airline pilots, improved scores on flight simulator tasks\(^16\).

There is substantial evidence for the hypothesis that ChEIs primarily act by improving cerebral blood flow (CBF). We will refer to this premise as the cholinergic–vascular hypothesis. A cholinergic augmentation of CBF could account for the global nature of the observed clinical improvement. It also serves to explain why this benefit is not limited to AD. Finally, it may clarify the intraindividual variation in response to treatment. These aspects will be further addressed in this article. The clinical relevance of this hypothesis is found in the recent recognition of the importance of vascular disease in the etiology of AD, in the frequent
occurrence of cerebrovascular comorbidity in AD, and in the growing interest in the use of ChEIs for the spectrum of vascular cognitive impairment.

The cholinergic–vascular hypothesis is based on the property of the brain’s cholinergic neurons to induce cerebral vasodilatation and to augment CBF\(^{17,18}\). These attributes of cholinergic neurons, together with the vascular effects of ChEIs, have been thoroughly investigated. This article will review the pertinent evidence for this hypothesis and discuss its implications for patient care and research. The classic cholinergic deficit hypothesis and the new cholinergic–vascular hypothesis can be mutually viable, and the interaction between these hypotheses will be addressed, with an additional comment on a possible interaction with the amyloid hypothesis.

**Evidence for the cholinergic–vascular hypothesis**

*Cholinergic Vasodilatory Innervation of Cerebral Blood Vessels*

The basal forebrain is the major source of brain cholinergic neurons. The hippocampus receives most of its input from the medial septal nucleus and the diagonal band of Broca, whereas the whole of the cerebral cortex is supplied by the nucleus basalis of Meynert (NBM)\(^{19}\). The most compelling evidence for the cholinergic–vascular hypothesis was found with the demonstration that these basal forebrain cholinergic neurons have projections to cerebral blood vessels. More precisely, in both rats and humans, arterioles in the frontoparietal cortex were found to contain perivascular cholinergic nerve terminals, and their origin could be traced back to the NBM\(^{20,21}\). When brains of AD patients were compared with those of age-matched controls, there was a loss of cholinergic innervation in cortical arterioles in AD, most prominently in the temporal lobes\(^{21}\).

The neurotransmitter for cholinergic neurons is Ach, which is also a potent vasodilator and can bind to two receptor types: nicotinic and muscarinic. Basal forebrain cholinergic neurons primarily involve muscarinic receptors. Evidence that Ach can induce vasodilatation as a postsynaptic neurotransmitter has come from the identification of these muscarinic receptors in perivascular astrocytes, smooth muscle cells, and endothelial cells, in cortical arterioles\(^{22,23}\).

In addition to these direct connections between NBM cholinergic neurons and cortical blood vessels, indirect connections involving nitrergic interneurons have been identified\(^{20,21,24}\). Cholinergic stimulation of these interneurons causes vasodilatation through the release of nitric oxide.
Stimulation and Inhibition of Cholinergic Neurons Modulates Cerebral Perfusion
Experiments in rats demonstrated that electrical and chemical stimulation of cholinergic neurons in the NBM results in a significant increase in CBF in several cortical areas.25–29 It is uncertain, however, if these stimuli were truly selective to the NBM. Other groups of neurons may have been activated as well. In contrast, inhibition of cholinergic neurons can be achieved with high selectivity. Following complete destruction of the NBM by a cholinergic immunologic toxin (192 immunoglobulin G–saporin), CBF decreased globally. Most severely affected regions included the posterior parietal and temporal regions (24%–40% decrease).30 It is remarkable that the regional distribution of hypoperfusion corresponded to the regions of the brain that are most prominently affected in AD.

The long-term effects of cholinergic inhibition were described in one study that found deposits of amyloid-betaprotein (aβ) in the cerebral vasculature 6 months after a lesion to the NBM.31 In patients with AD, deposits of aβ are found in the cortex in the form of neuritic plaques, but also around cortical vessels, especially in patients with vascular comorbidity.32,33 These data can be interpreted as follows: The cholinergic deficit promotes perivascular aβ-deposition, which could contribute to chronic brain hypoperfusion. Alternatively, vascular aβ-deposition may be a result of the chronic hypoperfusion that follows a cholinergic lesion.

Cholinergic and Anticholinergic Drugs Influence CBF
The effects of stimulation and inhibition of cholinergic neurons have also been assessed in pharmacological experiments. Scopolamine, an anticholinergic drug, blocks the binding of Ach to its muscarinic receptor. In young humans, scopolamine reduced frontal cerebral perfusion by 20%.34 An increase in CBF in various cortical regions was observed with cholinergic drugs (the ChEIs ertastigmine and physostigmine) in young and aged humans35. Moreover, physostigmine was able to restore CBF after it had been reduced by scopolamine36. In rats, rivastigmine reduced brain injury from hypoperfusion, indicating that autoregulation of CBF was improved.37

Effects of ChEI Treatment on CBF in AD
Computed tomography using radionuclides has provided information on regional changes in CBF in Alzheimer patients. Two early studies, looking at the effects of a single ChEI dose on CBF, found an increase in posterior parietotemporal and superior frontal perfusion.38,39 The longer-term outcome of treatment with ChEIs has been investigated extensively.40–48 Prospective studies in untreated patients
have found a strong correlation between clinical deterioration and progressive regional hypoperfusion. Consistently, patients who responded to treatment showed either improvement or stabilization of CBF\textsuperscript{49}. In contrast, nonresponders (those patients who demonstrated progressive cognitive deterioration with neuropsychological evaluation) had a progressive decline of CBF\textsuperscript{50}. Aside from AD, a rise in CBF after treatment with ChEIs was noted in patients with vascular dementia, dementia with Lewy bodies, and dementia of Parkinson’s disease, albeit in case reports and investigations in small numbers of patients\textsuperscript{50–53}.

The Increase in CBF Is Not an Effect of Increased Metabolism

An obvious thought is that the augmentation of CBF by ChEIs is a consequence of a regional increase in cerebral metabolism, which in turn is caused by cholinergic activation of cortical neurons. The available data, however, point toward a direct vascular effect. Blocking cortical neuronal activity did not prevent the increase in blood flow induced by cholinergic agonists\textsuperscript{54}. Electrical stimulation of the rat NBM augmented cortical CBF (up to 300% in frontal areas) without an increase in metabolic activity\textsuperscript{28,29}. Physostigmine increased CBF in both healthy young and aged humans, without a rise in cerebral glucose consumption\textsuperscript{35}. Other studies have also confirmed the lack of activation of glucose metabolism by physostigmine in rats and humans\textsuperscript{55,56}. In AD patients receiving ChEIs, the effects on CBF, paralleled by clinical effects, preceded effects on glucose metabolism by months\textsuperscript{45,57}.

Effects of CBF on Cognition

Central to the cholinergic–vascular hypothesis is the assumption that an increase in CBF improves cognition. To the best of our knowledge, direct evidence for this assumption is lacking, although the available circumstantial evidence is highly suggestive. In patients with carotid stenosis and impaired cerebral perfusion, restoration of normal cerebral perfusion by carotid endarterectomy improved cognitive functioning\textsuperscript{58,59}. In these studies, impairment in cerebrovascular reserve was used as a surrogate marker for chronic cerebral hypoperfusion, and postoperative restoration of cerebrovascular reserve was interpreted as an increase in cerebral perfusion. A recent investigation, however, found no improvement in cognition related to carotid endarterectomy\textsuperscript{60}. The cerebral hemodynamic status of these patients was not reported in this study. Therefore, an absence of cerebral hypoperfusion prior to surgery could explain the lack of cognitive benefit, which would be consistent with the previous investigations.
Two brief reports have mentioned an improvement in cognition after pacemaker implantation in older patients with bradycardia\textsuperscript{61,62}. In the first report, an improvement in CBF after implantation was correlated with an improvement in cognition. In the second report, the most striking effect on cognition was observed in three patients with dementia; in one of these patients, the dementia had fully reversed 6 months after implantation of the pacemaker.

The association between a reduced CBF and cognitive impairment has received much more attention. In the Rotterdam Study, a large population-based cohort study, individuals with cognitive decline were found to have lower CBF than were those individuals who had stable cognitive function in the previous years\textsuperscript{63}. Others have found that reduced CBF correlated with reduced cognitive functioning, regardless of the underlying brain disease\textsuperscript{64}. The mechanism for this relationship is likely to be the increasing sensitivity of neurons to ischemia or hypoperfusion with age\textsuperscript{65}. The evidence for the causal relationship between impairment in CBF, neuronal injury, and cognitive decline has recently been reviewed elsewhere\textsuperscript{17,66}.

**Clinical relevance**

*Interaction With the Vascular, Cholinergic, and Amyloid Hypotheses of AD*

The cholinergic–vascular hypothesis implies that the cholinergic deficit in AD not only affects cholinergic innervation of cortical neurons, but also leads to a loss of cholinergic innervation of cortical blood vessels. This vascular cholinergic deficit causes (regional) cerebral hypoperfusion, which in turn contributes to cognitive decline and neurodegeneration. Consequently, treatment with ChEIs may improve clinical functioning by augmenting cerebral perfusion. This mechanism offers an explanation for the intraindividual variation in response to treatment in AD. Recent research has focused on the vascular risk factors and the signs of overt vascular disease that are observed in many patients with AD\textsuperscript{17,66,67}. Cholinergic augmentation can lead to an increase in CBF only if the cerebral vasculature is able to respond with vasodilatation. The presence of severe microvascular deformity that is found in certain AD patients\textsuperscript{18}, as well as endothelial dysfunction from vascular disease or ischemia\textsuperscript{68,69}, could reduce or obstruct cholinergic vasodilatation. This obstruction would explain the lack of clinical response in a large subgroup of AD patients. Theoretically, these patients might benefit from the addition of medication aimed at improving vascular endothelial function, such as statins and angiotensin-converting enzyme (ACE) inhibitors.
Vasodilatation mediated by Ach is reduced by aβ, and aβ increases neuronal susceptibility to ischemia\textsuperscript{70-72}. Vice versa, ischemia promotes vascular and neuronal aβ deposition \textsuperscript{68,73}. Therapeutic interventions aimed at reducing aβ burden are thus likely to benefit from and be synergistic with strategies to improve cerebral perfusion [for review, see\textsuperscript{74}].

Because hypoperfusion contributes to the neuropathology of AD, the (partial) restoration of perfusion by ChEIs may slow neurodegeneration and hence progression of disease. Because there is no reason to assume that ChEIs halt cholinergic degeneration itself, the positive effect on CBF is likely to wane with the progressive loss of cholinergic neurons. Indeed, ChEI treatment stabilizes disease for a short period of time and may slow disease progression, but it fails to halt it, as has been observed in all trials in AD and, more recently, in Mild Cognitive Impairment\textsuperscript{9,11,75}. Combining ChEI therapy with strategies aimed at reducing cholinergic degeneration may hold promise to slow disease progression\textsuperscript{76,77}.

**Neurovascular Regulation**

The original cholinergic hypothesis and the new cholinergic–vascular hypothesis are not mutually exclusive. In contrast, they can coexist if we attribute a dual role to the cholinergic system: the coordination of neuronal activation and perfusion in cognitive tasks. This review has provided evidence that the cholinergic system is equipped to increase regional cerebral perfusion. Recent other reviews\textsuperscript{6,78} have summarized the large volume of evidence that this system also controls cognitive and attentional processes. Most experiments on this topic suggest that it acts as a central control system that shifts activity between cortical areas and regulates the process of attention, a prerequisite to perform cognitive tasks. Studies that explore patterns of cognitive activation use changes in cerebral hemodynamics as a surrogate measure for neuronal activity. For instance, functional magnetic resonance imaging (fMRI) measures the blood oxygen level dependent (or BOLD) signal, which depends on changes in deoxyhemoglobin. This practice is valid because changes in blood oxygenation occur almost instantaneously with neuronal activation\textsuperscript{79}. The striking temporal and spatial association of neuronal activation and increased blood flow fuels a speculative hypothesis on the physiological role of the cholinergic system. This system has the unique capability to activate regional cortical neurons through its cortical projections from the NBM and, at the same time, to direct blood flow to these neurons by simultaneously dilating the corresponding cortical microvessels through its vascular projections from that same NBM. This mechanism ensures that adequate nutrients (oxygen
and glucose) are directly available for activated neurons. This process of coupling of CBF with neuronal activation is described as functional hyperemia. Even though this mechanism is more complex than is suggested here, it is not unthinkably that the cholinergic system has a part in it. In AD, the cholinergic deficit will impair neurovascular regulation and lead to neuronal dysfunction and cognitive decline. Cerebrovascular disease and αβ deposition further contribute to this uncoupling by delaying the hemodynamic response following neuronal activation\textsuperscript{73,74,80}.

**Future research**
The validity and clinical relevance of this hypothesis need further confirmation in future studies. More precisely, such research could investigate whether nonresponders (AD patients who do not benefit from ChEIs) have an impaired vasodilatory response to ChEIs in comparison with responders. If so, a next step is to evaluate whether adding vascular therapy can improve this response. Recent developments in monitoring cerebral hemodynamics, such as fMRI, transcranial Doppler sonography, and near infrared spectroscopy, facilitate the noninvasive registration of the vascular effects of cholinergic augmentation in patients with dementia. For instance, transcranial Doppler sonography measures changes in CBF velocity, and near infrared spectroscopy measures changes in cerebral cortical tissue oxygenation, both with excellent temporal resolution and a relatively low cost. Both high temporal and partial resolutions for measuring CBF and brain tissue oxygenation are offered by fMRI\textsuperscript{81}. Specifically, arterial spin labeling techniques allow dynamic monitoring of changes in regional CBF, whereas diffusion tensor imaging may identify subtle changes in white matter integrity, which could be used as sensitive outcome parameters to record the effects of vascular treatment\textsuperscript{82}.

Regarding the concept of neurovascular regulation, it can be hypothesized that ChEIs will augment functional hyperemia in AD. If such an effect can indeed be observed, for instance with fMRI or positron emission tomography using a cortical stimulation paradigm, this may prove a valuable parameter to measure the complex response to pharmacotherapy in AD.
References


Cerebral perfusion in dementia: the role of cholinergic vascular innervation


