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COMMENTARY

Reversal of cerebral hypoperfusion: a novel therapeutic target for the treatment of AD/ADRD?

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Abstract Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) are emerging global health care crises and are primarily found among aging, especially with diabetes and hypertension. However, treatments based on current understanding have not been effective. The importance of vascular contribution to AD/ADRD has been recommended by the NINDS and NIA to be a focused research area. A recent study identified that phosphatidylinositol 4,5-bisphosphate (PIP_2) or its analogs could reverse cerebral hypoperfusion at the neurovascular unit in AD mice. Although more studies are needed to validate if PIP_2 analogs have sustained effects on CBF and can rescue cognitive impairment in AD/ADRD, and to elucidate and clarify whether targeting the retrograde (capillary-to-arteriole) pathway is beneficial to BBB function in AD/ADRD with poor CBF autoregulation, this finding provides exciting progress in understanding vascular contributions to AD/ADRD and suggests that reversal of cerebral hypoperfusion could be a novel therapeutic target for the treatment of AD/ADRD.

Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) are emerging global health care crises and are primarily found among aging, especially with diabetes and hypertension [1]. The prevailing view of AD is that a cholinergic deficiency, beta-amyloid (Aβ) accumulation, and hyperphosphorylation of tau protein all promote neurodegeneration and cognitive deficits. However, current therapy with cholinesterase inhibitors slows but does not prevent the progression of AD, and the failure of recent clinical trials targeting Aβ and tau pathways [2] has led the community to reconsider alternatives. Cognitive impairment and dementia (VCID), one of the major forms of ADRD, shares many pathological hallmarks with AD. The importance of vascular contribution to AD/ADRD has been increasingly recognized and was prioritized by the ADRD Summit 2016, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute on Aging (NIA), as part of the National Plan To Address AD, and recently recommended by the NIA to be a focused research area as the Milestone 2.S (https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-s).

It is now recognized that brain hypoperfusion is one of the causal factors of neurodegeneration that induces dementia not only in ADRD but also in AD individuals [3]. Thus, reversal of cerebral perfusion could be a potential novel therapeutic target for the treatment of AD/ADRD. Recent studies by the Nelson group [4] demonstrated that phosphatidylinositol 4,5-bisphosphate (PIP_2) or its analogs are such candidates. This proposition is strongly supported by new conceptual findings in their previous studies using Kir2.1 knockout mice and mathematical modeling [5, 6] that capillary endothelial cell (cEC) inward-rectifier K^+

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(Kir2.1) channels can be activated by neuronal action potential (AP)-evoked calcium mobilization and K^+ efflux in neurons, leading to an elevation in perivascular interstitial K^+, although whether this cEC Kir2.1 is also evoked by elevated extracellular K^+ released from astrocytes is unclear [5, 7]. The activation of cEC-derived Kir2.1 channels produces hyperpolarization at the neurovascular unit (NVU) that rapidly propagates, in a retrograde manner, along capillaries to upstream parenchymal arterioles (PAs) via gap junctions, resulting in robust vasodilation to increase local cerebral blood flow (CBF) to the neuronal activated area. Notably, these investigators found that the cEC-derived Kir2.1 activity is directly regulated by PIP_2 [8]. They found that the functional hyperemic response to whisker stimulation was impaired in 5xFAD mice in association with reduced Kir2.1 function in primary cECs isolated from this AD model. The neurovascular uncoupling and diminished Kir2.1 activity were rescued by a PIP2 analog. Intriguingly, PIP_2 levels are reduced in the brains of AD patients, possibly as a result of Aβ accumulation in cortical neurons [9]. The results collectively from animal and human studies suggest that PIP2 and its analogs are a potential novel target for the reversal of cerebral hypoperfusion for the treatment of AD/ADRD.

However, emerging evidence also supports that blood-brain barrier (BBB) dysfunction is another vascular hallmark and hypothesis in terms of the development of cognitive impairment in AD/ADRD [10]. BBB leakage results in micro- and macro-hemorrhages and rarefaction that lead to hypoperfusion in AD/ADRD. The BBB is formed by cECs, pericytes, astrocytes, and basement membrane. It can be damaged by many detrimental factors, including elevations in intraluminal pressure that are unrestrictedly transmitted from upstream PAs to the capillaries. This could be attributed to impaired CBF autoregulation that is exhibited in AD/ADRD individuals [10–12]. Major contributors for CBF autoregulation are vascular smooth muscle (VSMCs) and α-smooth muscle actin (α-SMA) positive pericytes on the pial arteries and PAs, which can restrict the rise in CBF from being delivered to the capillaries and NVU by vasoconstriction in response to elevations in blood pressure [13–15]. Both VSMCs and pericytes can receive K^+ signals and play vasodilation roles retrogradely along the cerebral vascular beds [5, 6, 16]. In this regard, whether PIP_2-Kir2.1 activation-induced upstream vasodilation might exacerbate BBB leakage and induce rarefaction rather than reverse hypoperfusion in AD/ADRD needs to be further investigated. One could argue that functional hyperemia increases local CBF in response to neuronal activation independent of fluctuations in perfusion pressure. However, the autoregulatory breakthrough points shift to lower pressures (120 mmHg), for example, in aging and diabetes-related dementia [11], implying that PIP_2-induced vasodilation may not simply have a beneficial role in individuals with impaired CBF autoregulation such as AD/ADRD. It might be possible to avoid these undesired side effects with careful consideration of the time frame to apply capillary vasodilatory therapy and by titrating the dose to monitor the extent of vasodilation in individuals that have impaired CBF autoregulation, based on the degree of BBB leakage in the progression of the disease. Moreover, whether chronic exogenous administration of PIP_2 and its agonists, as a substrate for phospholipase C (PLC), could enhance the production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) leading to vasoconstriction [17] also needs to be considered.

Additionally, capillary pericytes also have contractility that directs CBF [18] substantially although slowly [19]. These cells crosstalk with cECs and modulate the expression and function of tight junction proteins to maintain the integrity of the BBB via transforming growth factor-β1 (TGF-β1)/vascular endothelial growth factor (VEGF)/claudin 5 signaling pathways [11, 20]. Whether cEC Kir2.1 hyperpolarization affects this population of pericytes and their ability to regulate the distribution of capillary CBF and BBB function needs to be elucidated.

In summary, recent studies provided exciting progress in understanding vascular contributions to AD/ADRD and identified PIP_2 and its analogs as potential novel therapeutic approaches for the treatment of these devastating diseases. The effectiveness of this cEC-initiated Kir2.1 activation enhances local CBF at the NVU in response to neuronal activation. More studies are needed to validate if PIP_2 analogs have sustained effects on CBF and can rescue cognitive impairment in AD/ADRD. Additional studies are also needed to clarify whether targeting the retrograde (capillary-to-arteriole) pathway is beneficial to BBB function in AD/ADRD with poor CBF autoregulation and whether simultaneously targeting the retrograde and anterograde (arteriole-to-capillary) pathways along the cerebral vascular beds is needed to be more efficacious.

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Declarations

Conflict of interest The authors declare no competing interests.

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