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Perspectives

PERSPECTIVES

Capillary Inward-Rectifying K^+ Crippled in a Mouse Model of Alzheimer's Disease: Phosphatidylinositol 4,5-Bisphosphate to the Rescue!

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A Perspective on: "PIP_2 Improves Cerebral Blood Flow in a Mouse Model of Alzheimer's Disease"

Blood flow to the brain is precisely regulated to match the metabolic activity of neurons.[1] This process, dubbed neurovascular coupling, ensures the appropriate supply of oxygen, glucose, and other substrates necessary for proper brain function.[1] It has become apparent over the past two decades that cerebral blood flow is reduced, and neurovascular coupling is attenuated in a number of brain pathologies, including Alzheimer's disease (AD).[1–3] However, the time course of dysregulation of cerebral blood flow relative to the onset of cognitive impairment, the underlying mechanisms responsible for the dysregulation of blood flow, and, importantly, if reversal of impaired cerebrovascular function improves cognition in AD remains in question. Mughal et al.[4] in this issue of *Function* provide compelling evidence that reduced membrane phosphatidylinositol 4,5-bisphosphate (PIP_2), an established characteristic of Alzheimer's pathology,[5] inactivates brain capillary endothelial cell (EC) inward-rectifying K^+ ($K_{IR}2.1$) channels, resulting in attenuated neurovascular coupling in the whisker barrel cortex in a murine model of AD in which the mice express five mutant human genes associated with familial AD: three amyloid precursor protein (APP) genes (APPswe, APPflo, and APPlon) and two presenilin 1 (PS1 and PSEN1) genes (PSEN1 M146L and PSEN1 L286V; 5XFAD mouse).[6] The authors demonstrate that capillary EC $K_{IR}2.1$ channel function is crippled in this model system and that application of a PIP_2 analog in patch-clamp experiments completely rescues the channel function. Importantly, they go on to show that K^+-induced enhancement of red blood cell flux in capillaries, an in vivo test of capillary EC $K_{IR}2.1$ function, and neurovascular coupling in the somatosensory cortex invoked by whisker stimulation are likewise impaired in the 5XFAD mouse model of AD. Most excitingly, Mughal et al.[4] demonstrated rescue of capillary EC $K_{IR}2.1$ function and neurovascular coupling by intravenous (IV) administration of a PIP_2-analog. These data offer hope of dietary or pharmacological restoration of capillary EC membrane PIP_2 levels and restoration of ion channel function impaired by a reduction in PIP_2 in AD. The authors' findings also strongly support this group's contention that capillary EC $K_{IR}2.1$ channels serve as an important vascular sensor of extracellular $[K^+]$ released in proportion to neural and glial activity, providing a key signal that couples increases in local neuron electrical activity with increases in capillary blood flow to these active cells.

Several questions remain to be answered. First, what is the time course of capillary EC PIP_2 depletion relative to loss of neurons and, importantly, impaired cognitive function? How early are the capillary $K_{IR}2.1$ channels crippled in the progression of AD? Mughal et al.[4] used 12-month-old 5XFAD mice in their investigations. However, studies in this model have shown impaired cognition and loss of neurons as early as 4–5 months, while changes in cerebral blood flow appear at approximately 7 months.[7] Is capillary EC $K_{IR}2.1$ function also impaired at these time points? Second, does recovery of $K_{IR}2.1$ function by addition of exogenous PIP_2 restore or improve cognitive function in

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this model of AD and at what point does the PIP_2 have to be administered? Third, how selective was the IV administration of the PIP_2 analog to capillary EC? Decreased membrane PIP_2 also has been implicated in reduced synaptic transmission in AD models.[5,8] Did the IV administration of the PIP_2 analog improve signaling elsewhere in the neurovascular unit (neurons, astrocytes, etc.)? Fourth, while capillary EC $K_{IR}2.1$ function is impaired by loss of PIP_2.[4,9] capillary EC $TRPV_4$ function should be enhanced by loss of PIP_2.[9] Does, this imply that an increase in capillary EC $TRPV_4$ activity may contribute, somehow, to impaired neurovascular coupling in AD? Finally, it will be interesting to see if capillary $K_{IR}2.1$ is also crippled in human AD and whether $K_{IR}2.1$ function can be restored by PIP_2 supplementation. Obviously, additional research will be required to answer these and other questions that arise from this provocative study. Nonetheless, the paper by Mughal et al.[4] provides exciting new information that may help in our fight to combat cerebral pathologies, like AD.

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