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COMMENTARY

Communication breakdown: Impaired pericyte K_{ATP} channels in a model of Alzheimer's disease

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The brain requires a continuous supply of blood in proportion to its metabolic activity, a process that is disrupted in Alzheimer's disease. However, the mechanisms responsible for altered brain blood flow regulation in Alzheimer's disease remain poorly defined. In an earlier issue of *JGP*, Hariharan et al. (https://doi.org/10.1085/jgp.202614014) significantly add to our understanding of this pathology by showing that ATP-Sensitive K^+ (K_{ATP}) channels in thin strand pericytes on cerebral capillaries are compromised at 6–8 weeks in the 5X-FAD mouse model of Alzheimer's disease. They also confirmed that cerebral capillary endothelial inward rectifier K^+ (K_{IR}) channels are crippled and importantly show that this defect occurs at 2–4 months, before significant cognitive defects have been reported. Combined, these channelopathies severely attenuate electrical communication along cerebral capillaries, dampening blood flow regulation. These novel findings present new therapeutic targets to slow or possibly prevent the reduced cerebral blood flow in Alzheimer's disease, perhaps delaying or preventing cognitive decline. Like all scientific advances, they also open the door for new areas of research.

Normal brain function depends on a continuous, regulated supply of oxygen and glucose that is provided by blood flow. Under normal conditions, blood flow is matched to cerebral metabolism by the process termed neurovascular coupling, in which changes in neuronal activity (metabolic demand) result in changes in local blood flow to maintain a continuous supply of oxygen and glucose to support neuronal function. Interruption of this supply for even a few minutes leads to neuronal death, as exemplified by the devastating effects of stroke. Furthermore, it has become apparent over the past 15 years that compromised vascular function is a major contributor to ageing-related impairment in cognitive function and importantly contributes to dementias, including Alzheimer's disease (Anwer et al., 2026). Studies have shown that brain blood flow is reduced early in the evolution of Alzheimer's disease and that neurovascular coupling is impaired (Anwer et al., 2026). Thus, understanding the mechanisms responsible for these changes in vascular function in the development of Alzheimer's disease and related dementias is imperative.

Capillaries, the site where oxygen and glucose are exchanged between blood and neurons, and the endothelial cells and pericytes which comprise these microvessels, play a central role in the process of neurovascular coupling. They serve as a sensory nexus for detecting changes in their environment, as a pathway for electrical and other signal conduction to upstream arterioles, and as a site for tuning of capillary blood flow through contraction of abluminal pericytes that cover the surface of cerebral capillaries. Importantly, capillary endothelial cells and their overlying pericytes are electrically coupled by gap junctions, allowing electrical signals to be passed along the capillary wall from distal sites to the endothelium of upstream parenchymal arterioles (Fig. 1).

Capillary endothelial cells (Garcia and Longden, 2020) and their pericytes (Sancho et al., 2022; Sancho et al., 2024; Klug et al., 2023; Ferris et al., 2025; Harraz and Hashad, 2026; Tammaro and Hashitani, 2026; Xiang et al., 2026) express a diverse array of ion channels that participate in the local regulation of blood flow, and several ion channel–based mechanisms have been proposed to account for different aspects of capillary blood flow regulation and the process of neurovascular coupling (Longden et al., 2017; Longden et al., 2021; Thakore et al., 2021; Hariharan et al., 2022; Isaacs et al., 2024; Mughal et al., 2024) (Fig. 1). There is considerable evidence that activation of endothelial and/or pericyte ATP-sensitive K^+ channels (K_{ATP} channels) produces membrane hyperpolarization that is amplified by endothelial $K_{IR}2.1$ channels and conducted along capillary endothelial cells to upstream arteriolar endothelial cells, where it is transmitted to overlying smooth muscle cells to produce membrane hyperpolarization and deactivation of voltage-gated Ca^{2+} channels resulting in vasodilation and an increase in blood flow to the stimulated capillary (Hariharan et al., 2022; Sancho et al., 2022; Isaacs et al., 2024; Mughal et al., 2024; Fig. 1).

The study by Hariharan et al. (2026) in this issue of the *Journal of General Physiology* significantly adds to this body of

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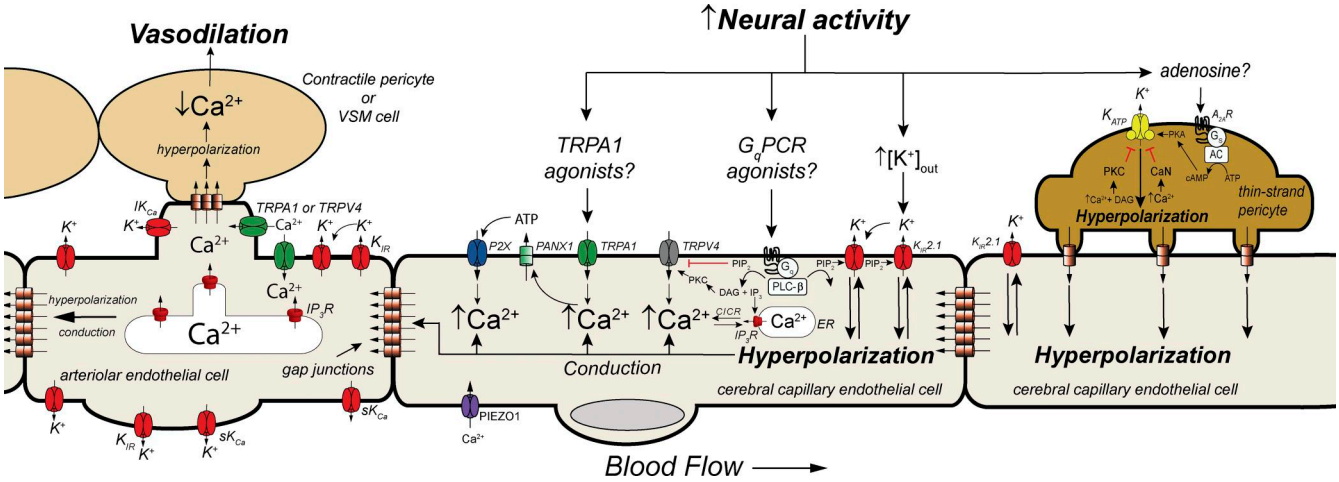


Figure 1. **Capillary ion channels and neurovascular coupling.** Schematic depicting a cross section through a cerebral capillary showing, from left to right, a smooth muscle cell (or contractile pericyte) coupled to an underlying endothelial cell by myoendothelial gap junctions, gap junction–coupled endothelial cells, and a thin-strand pericyte. The arteriolar endothelial cell is displayed expressing K_{IR} channels, small- and intermediate-conductance Ca^{2+}-activated K^+ channels (sK_{Ca} and IK_{Ca}, respectively), along with transient receptor potential vanilloid 4 (TRPV4) and transient receptor potential ankyrin 1 (TRPA1) channels located at myoendothelial junctions. The thin-strand pericyte and the endothelial cells are displayed with some of the ion channels that they express and their interactions with pericyte K_{ATP} channels. Potential regulation of pericyte K_{ATP} channels by PIP_2, PKC, and CaN is displayed in the thin-strand pericyte. Neuronal activity results in the release of several potential mediators, as shown. Adenosine (or other $G\alpha_S$-coupled receptor agonists) released from active neurons/astrocytes or produced from pannexin 1–released ATP acts at purinergic $adenosine_{2A}$ receptors ($A_{2A}R$) coupled to the $G\alpha_S$ protein (Gs)-adenylyl cyclase (AC)-cyclic adenosine monophosphate (cAMP)–PKA signaling pathway (Sancho et al., 2022). PKA phosphorylates and activates K_{ATP} channels (Tinker et al., 2018), resulting in pericyte hyperpolarization. This hyperpolarization is conducted through heterocellular gap junctions to underlying endothelial cells and, along with K^+ released from active neurons (Longden et al., 2017) and from the active K_{ATP} channels, activates capillary endothelial $K_{IR}2.1$ channels (Longden et al., 2017), amplifying the K_{ATP} channel-induced hyperpolarization and allowing the hyperpolarization to be conducted between electrically coupled endothelial cells, ultimately resulting in hyperpolarization of upstream smooth muscle cells (or contractile pericytes), deactivating their voltage-gated Ca^{2+} channels, leading to a decrease in intracellular Ca^{2+} and vasodilation. The K_{ATP} channel-induced hyperpolarization also will increase the electrochemical gradient for Ca^{2+} influx through Ca^{2+}-permeable ion channels such as TRPV4 channels activated by $G\alpha_{q/11}$ protein-coupled receptor-mediated signaling (Longden et al., 2021; Mughal et al., 2024), TRPA1 channels activated by yet to be defined neurally released agonists, and purinergic P2X receptors activated by ATP released through pannexin 1 (PANX1) channels (Thakore et al., 2021). The increased Ca^{2+} electrochemical gradient will increase intracellular Ca^{2+} signals produced by TRPV4 channels, TRPA1 channels, and P2X receptors. In addition, $G\alpha_{q/11}$ signaling will activate phospholipase Cβ (PLCβ), metabolizing PIP_2 to produce inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 will sensitize IP_3 receptors (IP_3R) to the elevated Ca^{2+}, resulting in Ca^{2+}-induced Ca^{2+} release (CICR) from intracellular stores. The increased Ca^{2+} and DAG will also activate PKC. Reduced membrane PIP_2 (as well as DAG-activated PKC) activates TRPV4 channels (Harraz et al., 2018) but inhibits $K_{IR}2.1$ (Harraz et al., 2018) and possibly K_{ATP} channels (Tinker et al., 2018), limiting the effects of $K_{IR}2.1$ and K_{ATP} channels on membrane potential. PKC activated by increased Ca^{2+} and DAG and Ca^{2+}-induced activation of CaN in pericytes may also inhibit or restrain K_{ATP} channel activity (Tinker et al., 2018). Adapted from Jackson (2022).

work by showing that the function of K_{ATP} channels in non-contractile, thin-strand pericytes in distal capillary segments is compromised in a time-dependent fashion in the mouse 5X-FAD model of Alzheimer's disease, in which there is overexpression of toxic amyloid β peptides and accelerated amyloid plaque formation. The study uses an aggressive model of Alzheimer's, which shows measurable behavioral deficits by 6–8 mo of age (Oakley et al., 2006; Richard et al., 2015; Tang et al., 2016; Forner et al., 2021). Hariharan et al. (2026) now show that by this age, thin-strand pericyte K_{ATP} channel function was substantially reduced, as assessed by sharp electrode recording of pericyte membrane potential in response to the K_{ATP} channel activator, pinacidil, or by blocking glucose transport with Bay-876. Previous studies have shown that capillary endothelial $K_{IR}2.1$ channel function is severely reduced at 12 mo in 5X-FAD mice (Mughal et al., 2021), a defect that can be corrected by addition of exogenous phosphatidylinositol bisphosphate (PIP_2) (Mughal et al., 2021). Hariharan et al. (2026) confirmed and importantly extended these findings by showing that endothelial $K_{IR}2.1$ function is compromised as early as 2–4 mo in this mouse model of Alzheimer's disease and that, as previously reported (Mughal et al., 2021), exogenous PIP_2 supplementation was able to restore $K_{IR}2.1$ channel function.

The findings of Hariharan et al. (2026) are significant because they provide a new and novel therapeutic target (pericyte K_{ATP} channels) that may help restore one mechanism involved in the local regulation of cerebral flow that is compromised early in the process of Alzheimer's disease. This study also significantly improves our understanding of the timeline of onset of deficits in capillary endothelial K_{IR} channels and pericyte K_{ATP} channels. However, as with all good science, the findings in this study raise additional questions that will require new experimental studies to answer.

First, the mechanisms responsible for the observed decrease in pericyte K_{ATP} channel function remain unknown. We do know that K_{ATP} channels are highly modulated and their function can be reduced by several mechanisms (Tinker et al., 2018). In other systems, for example, increased intracellular Ca^{2+} inhibits K_{ATP} channels by activating the Ca^{2+}-dependent protein phosphatase, calcineurin (CaN) (Tinker et al., 2018). In addition,

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PKC also inhibits K_{ATP} channels (Tinker et al., 2018), and it has been shown that amyloid β_{1-42}-induced ROS formation can activate PKC to influence other ion channels (Taylor et al., 2025). It will be interesting to see if there is a role for pericyte Ca^{2+} signaling, CaN, and/or PKC in the observed impairment of pericyte K_{ATP} channels in the 5X-FAD mouse model in future experiments.

Second, it is not known if and how the reported reduced activity of pericyte K_{ATP} channels and endothelial $K_{IR}2.1$ interact with other mechanisms of capillary signaling that have been reported (Longden et al., 2017; Longden et al., 2021; Thakore et al., 2021; Hariharan et al., 2022; Isaacs et al., 2024; Mughal et al., 2024). In particular, the electrocalcium coupling mechanism proposed by Mughal et al. (2024), which is driven by K_{ATP} and endothelial $K_{IR}2.1$ channel-mediated endothelial cell hyperpolarization, should be impaired. However, it is also known that amyloid β_{1-42} increases the activity of endothelial PIEZO1 channels, increasing Ca^{2+} entry and, perhaps, compensating for reduced endothelial cell hyperpolarization. Further research appears warranted.

Third, the studies of Hariharan et al. (2026) were all performed in components of the sensory cortex. Whether similar defects occur in other parts of the brain remains to be established. Studies in capillaries from other brain regions such as the hippocampus and cerebellum would seem to be important to determine if the observed defects in capillary endothelial KIR2.1 channel and thin-strand pericyte K_{ATP} channel function can be generalized.

Fourth, while it previously has been shown that capillary endothelial $K_{IR}2.1$ channels (Longden et al., 2017; Mughal et al., 2021; Mughal et al., 2024) and thin-strand pericyte K_{ATP} channels (Hariharan et al., 2022; Isaacs et al., 2024) contribute to different aspects of neurovascular coupling in wild-type mice, it is not known if the defect in pericyte K_{ATP} channel function observed in the present study actually impacts neurovascular coupling. Given the toolbox of alternative mechanisms that have been described to couple blood flow to neuronal function that may compensate for reduced pericyte K_{ATP} channel function (Longden et al., 2017; Longden et al., 2021; Thakore et al., 2021; Hariharan et al., 2022; Isaacs et al., 2024; Mughal et al., 2024), only additional experiments will provide answers to this question.

Fifth, it remains to be established if these defects in ion channel function translate specifically into cognitive impairment. Importantly, can prevention or resolution of these defects (by supplementing PIP_2, for example, to prevent decline in $K_{IR}2.1$ function) improve or delay cognitive decline in models of Alzheimer's disease?

Finally, it is also not known if the reported capillary channelopathies are common to all models of Alzheimer's disease and, importantly, in human Alzheimer's dementia. Arterial endothelial $K_{IR}2.1$ channel function is impaired in *3xTg-AD* mice at 16 mo of age (Hakim and Behringer, 2021), in APP23 mice at 18 mo of age (Taylor et al., 2022), and in APP mice at 7–10 mo of age (Lacalle-Aurioles et al., 2022). However, it is not known if these channels are compromised in capillaries and at earlier time points in these alternative models. It is also not known if PIP_2 supplementation restores K_{IR} channel function in other models of Alzheimer's disease. It is known that there are several ion channelopathies in human neurons from Alzheimer's patients (Cordaro et al., 2022; Bhoi et al., 2025) and alterations in K_{ATP} channel expression in neurons have been reported in humans with Alzheimer's disease and in mouse models of this disease (Grizzanti et al., 2023). However, whether capillary endothelial $K_{IR}2.1$ and pericyte K_{ATP} channels are inhibited in humans and the time course of this inhibition has yet to be studied.

Thus, the findings of Hariharan et al. (2026), while significantly adding to our understanding of amyloid β pathophysiology, have also opened new areas for investigation into capillary ion channel signaling in the brain microcirculation.

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