

Division of Medical Sciences

Seminar Series

2024 – 2025



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The roles of pericytes and glia in early Alzheimer's disease

It is common when studying Alzheimer's disease (AD) to focus mainly on generation of amyloid beta ($A\beta$) and hyperphosphorylated tau, and the changes of synaptic function and loss of cognitive power that they eventually produce. In this lecture I will emphasise $A\beta$ -driven factors that probably contribute early in the disease to later cognitive decline: a decrease of cerebral blood flow generated in part by microglia and a change in the properties of myelinated axons.

We previously showed that, in vivo in human AD and in a mouse model (APP^{NL-G-F}) of AD, capillaries (but not arterioles or venules) become constricted as a result of pericytes contracting (Nortley et al., 2019, Science). This was predicted to roughly halve cerebral blood flow. Human and mouse brain slice experiments suggested that the capillary constriction reflects oligomeric $A\beta$ evoking, in microglia and pericytes, generation of reactive oxygen species that then trigger the release of endothelin-1 (ET, possibly from endothelial cells or astrocytes) which evokes pericyte contraction. We have also shown that contraction of pericytes is amplified by a mechanism in which ET-evoked Ca^{2+} release from intracellular stores activates the TMEM16A chloride channel, generating a depolarization that opens voltage-gated calcium channels (Korte et al., 2022, JCI). We now report that giving to AD mice the voltage-gated calcium channel (CaV) blocker nimodipine in their drinking water from early in AD increased capillary diameter at pericytes, reduced leukocyte stalling at pericyte somata, improved CBF and attenuated brain hypoxia. $A\beta$ -evoked pericyte contraction in human cortical tissue was also greatly reduced by CaV block. Thus, awareness of the possibility of glia- and pericyte-mediated capillary constriction reveals new therapeutic targets to increase blood flow in AD, and possibly other neurological pathologies.

We previously showed that the conduction speed of myelinated axons can be tuned, not only by altering the number of wraps of myelin, but also by altering the dimensions of the node of Ranvier (Arancibia-Cárcamo et al., 2017 eLife). Furthermore, damage to the white matter has been suggested to be associated with AD. We now report that oligomeric $A\beta$ rapidly induces a lengthening of the node of Ranvier and a loss of myelin, which is expected to alter the conduction speed of the myelinated axon and thus disrupt neural circuit function. Understanding the mechanism of these effects may open up new therapeutic targets for early AD.

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Location: MSB 150