Exploring Ca2+ Signalling in Cerebrovascular Endothelial Cells: a Novel Player at the Neurovascular Unit

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Neurovascular coupling, also known as functional hyperemia, is the mechanism through which an increase in neuronal activity (NA) leads to the vasorelaxation of feeding arterioles, thereby redirecting local cerebral blood flow (CBF) to active neurons. Recent studies have revealed that mouse cerebrovascular endothelial cells can sense both neuronal and synaptic activity, thereby generating multiple vasorelaxant signals to increase CBF through an increase in intracellular Ca2+ concentration ([Ca2+]i). This lecture will extend these findings to the human brain microvascular endothelium by showing that it releases nitric oxide (NO), the primary vasorelaxing mediator within the human brain microcirculation, in response to neural and mechanical cues. Synaptically released neurotransmitters, such as glutamate, induce endothelial Ca2+ signals by activating both Group 1 metabotropic glutamate receptors, namely mGluR1 and mGluR5, and ionotropic NMDA receptors, thereby resulting in robust NO release. The endothelial Ca2+ response to glutamate is shaped by intracellular Ca2+ release through ER-embedded InsP3Rs and endolysosomal TPCs and is maintained by store-operated Ca2+ entry (SOCE). Intriguingly, pharmacological and genetic evidence suggests that mGluRs functionally interact with NMDARs to induce glutamate-induced Ca2+ signals. This lecture will further discuss unpublished data showing that the pharmacological and mechanical stimulation of the mechanosensitive Piezo1 channel also leads to intracellular Ca2+ signals and NO production. Thus, the human brain microvascular endothelium serves as a signal transduction platform for fine-tuning NO through NO release by integrating both parenchymal and blood-borne signals.