

Nitric oxide-dependent S-nitrosylation of Ca²⁺ homeostasis modulator 1 (CALHM1) channels coordinates neurovascular coupling through the control of astrocytic Ca²⁺ signaling

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Neuronal activity depends on the fine and timely regulation of cerebral blood flow by a mechanism known as neurovascular coupling. Neurotransmitters released during an increase in synaptic activity (e.g. glutamate) activate receptors in astrocytes located between neurons and parenchymal arterioles, which initiates a Ca²⁺ signaling that is propagated to the astrocytic-endfeet and evokes the release of vasodilator factors, leading to an increase in local blood flow. This process is coordinated among neighboring astrocytes, mainly, through gap junctions and ATP release via hemichannels. It has been proposed that release of NO, a potent vasodilator, from neurons, during an increase in synaptic activity, may be involved in neurovascular coupling. However, astrocytes express the Ca²⁺-dependent NO-synthetizing enzymes eNOS and nNOS and NO may be involved in the control of Ca²⁺ signals by direct S-nitrosylation of Ca²⁺ permeable channels such as connexins-based gap junction channels and hemichannels or pannexin-formed channels. Then, the participation of NO in the neurovascular coupling initiated by metabotropic glutamate receptor (mGluR) stimulation was assessed in primary cultures of astrocytes and rat brain slices. NO production, vasomotor response of brain cortex arterioles, changes in [Ca²⁺]_i and ATP release were evaluated. In addition, the activity of connexin hemichannels, pannexin channels and Ca²⁺ homeostasis modulator 1 (CALHM1) channels was also analyzed. Interestingly, the results indicate that NO and CALHM1 channels play an essential role in the astrocyte signaling that mediates neurovascular coupling. Stimulation of astrocytes mGluRs leads to NO-mediated activation of CALHM1 channels by S-nitrosylation, which evokes ATP release. The subsequent ATP-dependent purinergic receptor stimulation induces the opening of Cx43 hemichannels and Panx-1 channels, which contributes to the astrocytic Ca²⁺ signaling. These findings may provide clues to the design of new therapeutic strategies for the treatment of neurodegenerative diseases.

Biography

Xavier F Figueroa has completed his PhD from Pontifical Catholic University of Chile and Postdoctoral Studies from University of Virginia, Cardiovascular Research Center. Currently, he is Associate Professor at Pontifical Catholic University of Chile and is the Director of the Laboratory of Vascular Biology at the Department of Physiology. He has published more than 30 papers in reputed peer-reviewed journals, several of which have been highly cited. His lab combines cellular approaches with studies in intact and in vivo preparations to study the mechanisms involved in the control of microvascular function in peripheral tissues and in the brain.

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