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FUNCTIONAL HYPEREMIA: COMPARATIVE ANALYSIS OF SIGNALING PATHWAYS

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Neurovascular coupling (NVC) describes how the brain quickly increases blood flow to areas that are more active. This process ensures that active neurons get the glucose and oxygen they need, while also helping to remove waste products. This process, also known as functional hyperemia, ensures that the brain's blood supply matches its needs in accordance with metabolic demands. This system is managed by a neurovascular unit composed of neurons, astrocytes, pericytes, endothelial cells, and vascular smooth muscle cells. Because changes in blood oxygenation can be detected and converted into images, NVC forms the basis for diagnostic methods such as blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI).

For a long time, the established explanation for this was the astrocytic calcium-based model. According to this idea, astrocytes, a type of support cell, release vasoactive substances, such as prostaglandins, when stimulated by glutamate released from active neurons. Due to elevated levels of calcium inside astrocytes, the synthesis of vasodilators is triggered, which contracts and induces relaxation of the smooth muscle. An unknown mechanism was discovered during a comprehensive analysis conducted by Hosford and Gourine (2019). During their examination, which consisted of 11 studies in which neuronal nitric oxide synthase (nNOS) was selectively inhibited, they found that the NVC response dropped by only 64% on average. This observation suggests that a considerable portion remains unexplained. Therefore, there had to be another, faster mechanism running in parallel that did not depend on astrocytic calcium.

When comparing the old, slow, diffusion-dependent view with what Krolak et al. (2025) uncovered, they showed that arterial endothelial cells are linked by gap junctions made of connexins 37 and 40, creating an electrical route that passes hyperpolarization at approximately 4 mm/s, a speed that is impossible for chemical signaling alone. This rapid directional vasodilation fits perfectly with the missing 36 % of the response. Later work has filled in more details: Kovacs-Oller et al. (2020) found that a small, focused light stimulus strengthens pericyte-endothelial connections toward the upstream artery, and local nitric oxide tells them the direction. Burma et al. (2024) recorded brain waves, capillary oxygen levels, and artery flow at the same time in human volunteers revealing one-way, feed-forward relationship – neural and microvascular activity came first, then the upstream artery responded. Other studies have examined pericyte electrical signaling (Longden et al., 2025), ion channels in capillaries (Hashad et al., 2025), and the development of NVC across the lifespan (Khartabil et al., 2026), all of which provide supporting evidence for the presence of a faster pathway.

After compiling all of this evidence, it is clear that NVC relies on two different but complementary pathways. One is a slower, chemically driven astrocyte route. The other is the fast, electrical endothelial gap-junction pathway, the “highway” that sets both the speed and the reach of vasodilation. The discovery finally part of the response that had been an unanswered question for years. When this endothelial pathway is disrupted, it probably adds to the cerebrovascular manifestations seen in common illnesses such as diabetes and Alzheimer’s disease. The ideas presented in this review showcase new possibilities for diagnostic methods and treatment approaches focused on maintaining cerebrovascular health.