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Review Paper

Beyond Blood Flow: Cellular and Molecular Dimensions of Neurovascular Coupling

Tiffany J. McGehee*, Carrie R. McKee, Georgina W. Ahner, Ashley D. Schlater
Department of Neurology and Pediatric Neurology, Mexico

***Corresponding Author:** Tiffany J. McGehee, Department of Neurology and Paediatric Neurology, Mexico
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Abstract
Neurovascular coupling (NVC) refers to the tightly regulated relationship between neuronal activity and cerebral blood flow, ensuring that active brain regions receive adequate oxygen and nutrients. This phenomenon forms the physiological basis of functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS). Over the past two decades, advances in cellular neuroscience, vascular biology, and imaging technologies have expanded the classicalneuron-centric view of NVC to a more integrative framework involving glial cells, vascular smooth muscle cells, pericytes, and endothelial signaling. This review synthesizes current understanding of the mechanisms underlying neurovascular coupling, highlighting cellular contributors, molecular mediators, spatial and temporal dynamics, and alterations observed in neurological and neurovascular disorders. Emphasis is placed on emerging concepts that reshape traditional models and their implications for brain health and disease

Introduction
The human brain, despite representing only a small fraction of total body mass, consumes a disproportionately large share of oxygen and glucose. Because neurons possess limited energy reserves, continuous and precise regulation of cerebral blood flow (CBF) is essential formaintaining normal brain function. Neurovascular coupling describes the process by which increases in neuronal activity lead to rapid and localized increases in blood flow, a phenomenon often termed functional hyperemia directly signaled process integrating neuronal firing, synaptic transmission, glial modulation, and vascular responsiveness. Understanding this complexity is critical not only for basic neuroscience but also for the correct interpretation of neuroimaging signals and for elucidating mechanisms underlying neurological diseases

Historical Perspectives and Conceptual Evolution

Early observations of activity-dependent changes in cerebral circulation date back to the late nineteenth century, when researchers noted increased blood flow in brain regions engaged during sensory stimulation. With the advent of modern imaging methods in the late twentieth century, especially fMRI, neurovascular coupling gained renewed attention as the physiological substrate of blood-oxygen-level-dependent (BOLD) signals. Initial models emphasized a direct neuron-to-vessel signaling pathway, often mediated by metabolic by-products such as carbon dioxide or potassium ions. While these factors contribute to vascular responses, they fail to fully account for the speed, specificity, and adaptability of functional hyperemia. Contemporary frameworks now recognize NVC as an emergent property of the neurovascular unit, a structural and functional ensemble composed of neurons, astrocytes, endothelial cells, pericytes, smooth muscle cells, and extracellular matrix components.

Cellular Components of the Neurovascular Unit
Neurons

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Neurons initiate neurovascular coupling by generating electrical and synaptic activity. Neurotransmitter release, particularly glutamate, plays a central role in signaling metabolic demand. Beyond synaptic transmission, neurons can release vasoactive substances that influence vascular tone either directly or indirectly through intermediary cells

Astrocytes

Astrocytes occupy a strategic position between synapses and blood vessels, with end-feet that envelop much of the cerebral vasculature. They are now considered key regulators of NVC. In response to neuronal activity, astrocytes exhibit intracellular calcium signaling that can trigger the release of vasoactive molecules. These signals enable astrocytes to translate synaptic activity into vascular responses, modulating blood flow with spatial precision.

Endothelial Cells

Endothelial cells line the interior of cerebral blood vessels and actively participate in vascular signaling. They produce factors that regulate vasodilation and vasoconstriction and can propagate signals along the vascular tree. Endothelial dysfunction is increasingly recognized as a contributor to impaired neurovascular coupling in disease states

Pericytes and Vascular Smooth Muscle Cells

Pericytes, located on capillaries, and smooth muscle cells, found on arterioles, are contractile elements that directly control vessel diameter. Their responses to neuronal and glial signals determine the magnitude and timing of blood flow changes. The relative contributions of pericytes versus smooth muscle cells remain an area of active investigation.

Molecular and Signaling Mechanisms

Neurovascular coupling relies on a diverse array of molecular mediators. Neurotransmitters released during synaptic activity can activate receptors on astrocytes and neurons, initiating signaling cascades. These cascades often involve intracellular calcium dynamics and the synthesis or release of vasoactive agents. Key classes of mediators include gaseous messengers, lipid derivatives, and ions. These substances can act locally or diffuse to nearby vascular cells, producing either vasodilation or vasoconstriction depending on context. Importantly, the balance between these opposing effects allows fine-tuning of cerebral blood flow in response to varying patterns of neural activity.

Spatial and Temporal Dynamics of Neurovascular Coupling

Neurovascular responses are characterized by remarkable spatial specificity, often confined to microvascular territories serving active neuronal populations. Temporally, coupling occurs on the order of seconds, enabling rapid adaptation to changing functional demands

Neurovascular Coupling in Health and Disease

Disruption of neurovascular coupling has been implicated in a wide range of neurological conditions, including stroke, neurodegenerative diseases, epilepsy, and traumatic brain injury. In these contexts, impaired signaling within the neurovascular unit can lead to mismatches between neuronal activity and blood supply, exacerbating tissue damage and functional decline. Age-related changes in vascular structure and cellular signaling also affect NVC efficiency, potentially contributing to cognitive impairment. As a result, neurovascular coupling is increasingly viewed not only as a physiological mechanism but also as a therapeutic target.

Implications for Functional Neuroimaging

Because functional neuroimaging techniques rely on hemodynamic responses as proxies for neuronal activity, a detailed understanding of neurovascular coupling is essential. Variations in NVC across individuals, brain regions, or disease states can complicate the interpretation of imaging signalsIntegrating insights from cellular and molecular studies into imaging analysis may improve the accuracy of brain mapping and enhance the diagnostic and prognostic value of functional imaging modalities

Future Directions

Despite substantial progress, many questions remain regarding the precise mechanisms and regulatory principles of neurovascular coupling. Emerging imaging technologies, genetic tools, and computational models offer new opportunities to dissect NVC with unprecedented resolutionFuture research is likely to focus on cell-type-specific contributions, interactions between metabolic and electrical signaling, and the translation of basic findings into clinical applications. A more complete understanding of neurovascular coupling will deepen insight into brain function and inform strategies for preventing and treating neurological disease

Conclusion

Neurovascular coupling represents a fundamental mechanism by which the brain aligns its metabolic supply with functional demand. Once considered a simple, neuron-driven process, it is now recognized as

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a complex, dynamic interaction within the neurovascular unit. Continued investigation into itscellular and molecular foundations will not only refine interpretations of brain imaging but also illuminate pathways implicated in neurological disorders, underscoring the central role of vascular health in brain function

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