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The neurovascular unit: A key player in stroke pathogenesis.

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Introduction

The neurovascular unit represents a highly integrated network of cellular and molecular components that maintain the delicate balance between neuronal activity, vascular function, and metabolic support in the brain. It is composed of neurons, astrocytes, microglia, endothelial cells, pericytes, vascular smooth muscle cells, and the extracellular matrix, all working together to ensure proper cerebral blood flow, blood–brain barrier integrity, and homeostasis of the neural microenvironment. In health, this intricate system allows rapid communication between neurons and blood vessels, adjusting blood supply to match local metabolic demands—a process known as neurovascular coupling. In disease, particularly in stroke, disruption of the neurovascular unit's tightly regulated interactions plays a central role in the pathogenesis, progression, and outcome of brain injury [1].

Stroke, whether ischemic or hemorrhagic, is fundamentally a vascular event that immediately challenges the stability and function of the neurovascular unit. In ischemic stroke, arterial occlusion leads to a sharp drop in local cerebral blood flow, depriving brain tissue of oxygen and glucose. Neurons in the ischemic core rapidly lose their ability to maintain ion gradients, leading to depolarization, calcium overload, excitotoxic glutamate release, and activation of destructive enzymatic cascades. Surrounding this core is the ischemic penumbra, an area with reduced but still salvageable blood flow, where neurovascular unit dysfunction plays a decisive role in determining tissue fate. If neurovascular integrity can be preserved or restored, the penumbra has the potential to recover; if not, it progresses to irreversible infarction [2].

One of the earliest consequences of ischemia is endothelial dysfunction within the neurovascular unit. Endothelial cells normally form the backbone of the blood–brain barrier, regulating permeability and protecting the brain from potentially harmful blood-borne substances. Ischemia rapidly disrupts endothelial cell tight junctions, increases vesicular transport, and activates inflammatory signaling pathways. This results in increased blood–brain barrier permeability, allowing plasma proteins, leukocytes, and other circulating factors to enter the brain parenchyma. The ensuing vasogenic edema raises intracranial pressure and further compromises microvascular perfusion, worsening ischemic injury [3].

Astrocytes, which normally support neurons and maintain extracellular ion and neurotransmitter balance, undergo reactive changes during stroke. Under normal circumstances, their endfeet cover the majority of the vascular surface, helping regulate blood flow and contributing to blood–brain barrier function. In stroke, astrocytic swelling due to

cytotoxic edema compresses microvessels, impairing perfusion in the penumbra. Reactive astrocytes also release inflammatory mediators, reactive oxygen species, and matrix metalloproteinases, which further degrade the extracellular matrix and tight junction proteins, aggravating barrier breakdown [4].

Microglia, the resident immune cells of the brain, rapidly activate in response to ischemia. In the acute phase, microglial activation can be protective by removing debris and releasing neurotrophic factors. However, excessive or prolonged activation skews microglia toward a pro-inflammatory phenotype, producing cytokines, chemokines, and nitric oxide that exacerbate neuronal injury. Activated microglia can also recruit peripheral immune cells into the brain, amplifying inflammatory damage within the neurovascular unit [5].

Conclusion

In conclusion, the neurovascular unit is central to the pathogenesis of stroke, serving as the interface between neuronal and vascular systems that determines the brain's response to ischemic or hemorrhagic injury. Disruption of the intricate interactions among neurons, glia, endothelial cells, pericytes, smooth muscle cells, and the extracellular matrix sets in motion a cascade of events that amplify tissue damage and influence recovery. Preservation and restoration of neurovascular unit function represent critical therapeutic goals, complementing existing reperfusion strategies. A deeper understanding of neurovascular unit biology holds great promise for improving stroke prevention, acute treatment, and long-term rehabilitation, ultimately reducing the devastating impact of this disease on patients and society.

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