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NEUROVASCULAR UNIT DYSFUNCTION IN NEUROLOGICAL DISORDERS: MECHANISMS AND THERAPIES

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Abstract
The neurovascular unit (NVU) is a specialized multicellular system composed of brain endothelial cells, pericytes, vascular smooth muscle cells, astrocytes, neurons, microglia, and extracellular matrix. It maintains blood–brain barrier (BBB) integrity, regulates cerebral blood flow, supports neuronal metabolism, and contributes to clearance of metabolic waste. Increasing evidence indicates that NVU dysfunction is not simply a consequence of neurological disease but may represent an early mechanism contributing to disease progression. Endothelial dysfunction, pericyte loss, impaired neurovascular coupling, astrocytic dysfunction, neuroinflammation, and extracellular matrix degradation can lead to BBB disruption, cerebral hypoperfusion, and neuronal injury. These mechanisms are implicated in ischemic stroke, Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, cerebral small-vessel disease, traumatic brain injury, epilepsy, and brain tumors. This review summarizes the major structural and physiological features of the NVU, the mechanisms underlying its dysfunction, its role in neurological disorders, and emerging therapeutic approaches aimed at restoring neurovascular integrity.

Keywords: Neurovascular unit, Blood–brain barrier, Neurovascular coupling, Cerebral microcirculation, Neuroinflammation, Pericytes, Neurodegeneration.

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Introduction

1. Structure and Physiological Functions of the Neurovascular Unit

The neurovascular unit integrates cerebral blood vessels with surrounding neural and glial cells to maintain CNS homeostasis. Its principal components include brain endothelial cells, pericytes, vascular smooth muscle cells, astrocytes, neurons, microglia, and the vascular basement membrane (Iadecola, 2017; Schaeffer and Iadecola, 2021).

Brain endothelial cells form the structural basis of the blood–brain barrier. They contain highly developed tight and adherens junctions, have low rates of transcytosis, and express selective transporters such as GLUT1 and LAT1 together with efflux systems including P-glycoprotein (Daneman and Prat, 2015; Profaci et al., 2020). These properties restrict uncontrolled entry of circulating molecules while allowing regulated transport of nutrients and metabolites.

Pericytes are embedded within the vascular basement membrane and provide structural support to capillaries. They regulate endothelial barrier properties, vascular stability, and microvascular perfusion (Armulik et al., 2010; Bell et al., 2010). Vascular smooth muscle cells surround larger cerebral arteries and arterioles, controlling vascular tone and cerebral autoregulation.

Astrocytes connect neurons with the microvasculature through their perivascular end-feet. They contribute to BBB maintenance, ion and water regulation, metabolic support, and neurovascular coupling. Aquaporin-4 (AQP4) channels concentrated at astrocytic end-feet also participate in brain water movement and interstitial waste clearance (Iliff et al., 2012).

Neurons regulate local vascular responses according to metabolic demand, while microglia provide immune surveillance and participate in vascular remodeling and inflammatory responses (Kaplan et al., 2020; Thurgur and Pinteaux, 2019). Together, these components form a dynamic system in which vascular and neural function are continuously coordinated.

2. Neurovascular Coupling and Blood–Brain Barrier Function

One of the major functions of the NVU is neurovascular coupling, through which neuronal activity produces a local increase in cerebral blood flow. Increased neuronal firing activates signaling pathways involving nitric oxide, prostaglandins, epoxyeicosatrienoic acids, potassium ions, and other vasoactive

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mediators. These signals act on vascular smooth muscle cells and pericytes, producing local vasodilation and functional hyperemia (Filosa et al., 2016; Iadecola, 2017).

The NVU also maintains the BBB, which protects neural tissue from fluctuations in the systemic circulation. Tight junction proteins such as claudin-5, occludin, and ZO-1 limit paracellular diffusion, while low endothelial transcytosis restricts nonspecific movement of macromolecules (Daneman and Prat, 2015; Sweeney et al., 2019). Transport proteins provide controlled entry of glucose, amino acids, and other essential substances, whereas efflux transporters remove many potentially harmful compounds.

Communication between NVU cells is controlled by several signaling pathways. Wnt/β-catenin signaling supports BBB development and endothelial stability, while angiopoietin/Tie2 signaling promotes vascular maturation and reduces inflammation. In contrast, excessive VEGF signaling, endothelin-1, oxidative stress, and inflammatory mediators can destabilize endothelial junctions and increase vascular permeability (Liebner et al., 2018; Zhao et al., 2015).

The NVU therefore functions as more than a physical barrier. It simultaneously controls blood flow, nutrient transport, immune surveillance, extracellular fluid composition, and communication between neurons and blood vessels.

3. Mechanisms of Neurovascular Unit Dysfunction

NVU dysfunction develops through interconnected processes affecting endothelial cells, mural cells, astrocytes, and immune cells. A major initiating mechanism is endothelial dysfunction, characterized by disruption of tight junction proteins, increased transcytosis, oxidative stress, and inflammatory activation. BBB breakdown allows plasma proteins and inflammatory mediators to enter the CNS and further activate resident immune cells (Zlokovic, 2011; Sweeney et al., 2019).

Pericyte dysfunction is another important mechanism. Pericyte loss or pathological contraction can increase BBB permeability and reduce capillary perfusion. In conditions such as Alzheimer's disease and ischemic stroke, pericyte dysfunction has been associated with microvascular hypoperfusion and impaired capillary blood flow (Bell et al., 2010; Kisler et al., 2017; Nortley et al., 2019).

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Astrocytic dysfunction contributes through loss of normal end-foot organization, altered AQP4 distribution, impaired ion regulation, and reduced metabolic support. These changes can disturb extracellular fluid balance and potentially impair clearance of pathological proteins (Iliff et al., 2012).

Neuroinflammation further amplifies NVU injury. Activated microglia and endothelial cells release cytokines such as TNF-α, IL-1β, and IL-6, while inflammatory signaling promotes leukocyte adhesion and infiltration. Matrix metalloproteinases, particularly MMP-2 and MMP-9, can degrade extracellular matrix components and junctional proteins, further weakening the BBB (Liebner et al., 2018; Yang et al., 2019).

Oxidative and mitochondrial stress represents a common final pathway. Excess reactive oxygen species can reduce nitric oxide bioavailability, damage cellular membranes and proteins, and impair ATP production. The resulting vascular dysfunction, inflammation, and metabolic failure create a self-reinforcing cycle of BBB disruption and neuronal injury.

4. NVU Dysfunction Across Neurological Disorders

NVU dysfunction is involved in both acute and chronic neurological disorders, although the dominant mechanisms differ between diseases.

In ischemic stroke, interruption of cerebral blood flow rapidly produces energy failure, excitotoxicity, endothelial injury, and BBB disruption. Pericyte contraction may contribute to the microvascular no-reflow phenomenon even after successful arterial recanalization. Subsequent oxidative stress, inflammation, and matrix metalloproteinase activation increase vascular permeability and contribute to cerebral edema and hemorrhagic transformation (Yang et al., 2019).

In Alzheimer's disease, BBB dysfunction and pericyte degeneration can appear early in disease progression. Human studies have demonstrated increased BBB permeability and elevated soluble PDGFRβ, a marker associated with pericyte injury, in individuals with cognitive impairment (Montagne et al., 2015; Nation et al., 2019). APOE4 can further promote vascular dysfunction through inflammatory and MMP-dependent mechanisms (Montagne et al., 2020). At the same time, impaired endothelial transport and vascular dysfunction may reduce

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amyloid-β clearance, creating a feedback loop between vascular injury and protein accumulation (Yamazaki and Kanekiyo, 2017).

In Parkinson's disease, BBB disruption and neurovascular inflammation have been reported in affected brain regions. α-Synuclein pathology, microglial activation, and inflammatory signaling may impair endothelial integrity and contribute to the vulnerability of dopaminergic neurons (Sweeney et al., 2019).

In multiple sclerosis, endothelial activation is central to immune-cell migration into the CNS. Increased expression of adhesion molecules such as VCAM-1 and ICAM-1 facilitates lymphocyte interaction with the BBB, while inflammatory mediators and matrix metalloproteinases promote barrier disruption and lesion development (Obermeier et al., 2013; Engelhardt et al., 2017).

Cerebral small-vessel disease involves chronic injury to small arteries, arterioles, capillaries, and venules. Vascular remodeling, endothelial dysfunction, basement membrane abnormalities, and impaired perivascular fluid regulation contribute to white matter lesions, lacunar infarction, and cognitive impairment (Wardlaw et al., 2019).

NVU dysfunction is also important in traumatic brain injury, epilepsy, and brain tumors. Mechanical injury can rapidly disrupt the BBB and initiate secondary inflammatory and oxidative processes. In epilepsy, albumin leakage into the brain can alter astrocytic signaling and ion regulation, potentially increasing neuronal excitability. In glioblastoma, abnormal tumor-associated vessels form a dysfunctional blood-tumor barrier characterized by increased permeability, disorganized angiogenesis, and severe vasogenic edema (Marchi et al., 2004; Liebner et al., 2018).

5. Therapeutic Perspectives and Future Directions

Because NVU dysfunction involves several interacting cell types, effective treatment may require strategies that target vascular, inflammatory, and neuronal mechanisms simultaneously. Current clinical therapies for ischemic stroke, including thrombolysis and mechanical thrombectomy, primarily restore cerebral perfusion, but preservation of the microvascular barrier remains an important therapeutic objective.

Experimental approaches include stabilization of endothelial junctions, inhibition of pathological MMP activity, reduction of oxidative stress, and restoration of

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pericyte function. Modulation of pathways such as CypA–NF-κB–MMP-9, Wnt/β-catenin, and angiopoietin/Tie2 has shown potential in experimental models (Montagne et al., 2020; Zhao et al., 2015). Antioxidant and anti-inflammatory strategies are also being investigated to reduce secondary NVU damage.

An additional area of development is BBB-targeted drug delivery. Nanoparticles, liposomes, extracellular vesicles, and receptor-mediated transport systems targeting receptors such as the transferrin receptor or LRP1 may improve delivery of therapeutic molecules to the CNS without directly disrupting the BBB (Profaci et al., 2020).

Translation remains challenging because animal models often do not reproduce the age, vascular risk factors, and cellular complexity of human neurological disease. New approaches including human iPSC-derived NVU models, organ-on-a-chip systems, single-cell transcriptomics, spatial transcriptomics, and high-field MRI may improve disease modeling and identification of patient-specific therapeutic targets (Langen et al., 2019; Schaeffer and Iadecola, 2021).

Conclusion

The neurovascular unit is a central regulator of cerebral homeostasis, integrating vascular, neuronal, glial, and immune functions. Its dysfunction can impair cerebral blood flow, disrupt the BBB, promote neuroinflammation, and contribute to neuronal injury across a wide range of neurological diseases.

Recognition of NVU dysfunction as an active component of disease pathogenesis has expanded the therapeutic focus beyond neurons alone. Future treatments will likely combine vascular protection, anti-inflammatory strategies, metabolic support, and targeted drug delivery. Continued development of human-based experimental models and advanced neuroimaging may help translate these concepts into effective therapies for neurological disorders.

References

1. Armulik, A., et al. (2010). Pericytes regulate the blood-brain barrier. Nature, 468, 557-561.
2. Bell, R. D., et al. (2010). Pericytes control key neurovascular functions and hematogenous immune cell infiltration in the brain. Neuron, 68, 409-427.

Ideal Journal of Multidisciplinary Research
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Website: https://researchiapress.com

3. Daneman, R., & Prat, A. (2015). The blood-brain barrier. Cold Spring Harbor Perspectives in Biology, 7, a020412.
4. Engelhardt, B., et al. (2017). The neurovascular unit and the lymphatic system in neuroinflammation. Nature Immunology, 18, 123-132.
5. Filosa, J. A., et al. (2016). Beyond the myogenic response: neurovascular functioning in health and disease. The Journal of Physiology, 594, 4461-4479.
6. Iadecola, C. (2017). The neurovascular unit coming of age. Neuron, 96, 17-42.
7. Iliff, J. J., et al. (2012). A paravascular pathway facilitates CSF flow through the CNS parenchyma and the clearance of interstitial solutes. Science Translational Medicine, 4, 147ra111.
8. Kaplan, L., Chow, B. W., & Gu, C. (2020). Neuronal regulation of the blood-brain barrier during homeostasis and disease. Neuron, 107, 289-301.
9. Kisler, K., et al. (2017). Cerebral blood flow regulation and neurovascular unit dysfunction in Alzheimer's disease. Nature Reviews Neuroscience, 18, 419-434.
10. Langen, U. H., Ayloo, S., & Gu, C. (2019). Development and cell biology of the blood-brain barrier. Annual Review of Cell and Developmental Biology, 35, 201-213.
11. Liebner, S., et al. (2018). Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathologica, 135, 311-336.
12. Marchi, N., et al. (2004). Peripheral markers of blood-brain barrier damage. Clinica Chimica Acta, 342, 1-12.
13. Montagne, A., et al. (2015). Blood-brain barrier breakdown in the aging human hippocampus. Neuron, 85, 296-302.
14. Montagne, A., et al. (2020). APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature, 581, 71-76.
15. Nation, D. A., et al. (2019). Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nature Medicine, 25, 270-276.
16. Nortley, R., et al. (2019). Amyloid-β oligomers constrain human capillaries through pericyte contraction. Science, 365, eaav9518.
17. Obermeier, B., Daneman, R., & Ransohoff, R. M. (2013). Development, maintenance and disruption of the blood-brain barrier. Nature Medicine, 19, 1584-1596.

Ideal Journal of Multidisciplinary Research
ISSN (E): 3054-3339
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Website: https://researchiapress.com

18. Profaci, C. P., et al. (2020). The blood-brain barrier in health and disease. Journal of Experimental Medicine, 217, e20190062.
19. Rust, R., et al. (2019). Neurovascular remodeling in stroke recovery. Trends in Neurosciences, 42, 818-830.
20. Schaeffer, S. M., & Iadecola, C. (2021). Revisiting the neurovascular unit. Nature Neuroscience, 24, 1198-1209.
21. Sweeney, M. D., et al. (2019). Blood-brain barrier: From physiology to disease and back. Physiological Reviews, 99, 21-78.
22. Thurgur, H., & Pinteaux, E. (2019). Microglia in the neurovascular unit: policing the frontier. Neural Regeneration Research, 14, 1341-1347.
23. Wardlaw, J. M., Smith, C., & Dichgans, M. (2019). Small vessel disease: mechanisms and clinical implications. The Lancet Neurology, 18, 684-696.
24. Yamazaki, Y., & Kanekiyo, T. (2017). Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International Journal of Molecular Sciences, 18, 1965.
25. Yang, C., et al. (2019). Neuroinflammatory mechanisms of blood-brain barrier damage in ischemic stroke. American Journal of Physiology-Cell Physiology, 316, C135-C153.
26. Zhao, Z., et al. (2015). Establishment and dysfunction of the blood-brain barrier. Cell, 163, 1064-1078.
27. Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nature Reviews Neuroscience, 12, 723-738.