The Neurovascular Unit in Health and Disease

Introduction

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Over the past 10 years, study of the blood vessel in cerebrovascular disease has expanded from consideration of only endothelial cells to include interactions with neurons, astrocytes, pericytes, and extracellular matrix. The role of other cells in the pathobiology of cerebral blood vessels has been encompassed under the term “neurovascular unit (NVU).” This session brings together a series of papers on the role of the NVU in stroke and neurodegenerative diseases. The endothelial cell remains central to the NVU, but its function is regulated by input from adjacent pericytes, astrocytes, and neurons. The extracellular matrix and the matrix-degrading enzymes and inhibitors play a key role at the basal lamina and the cell surface in the regulation of cell signaling. Much has been learned about the function of astrocytes, which rapidly transduce information between the microenvironment and other brain cells and the macrophage-like pericytes in effecting changes at the cerebral capillary level. The presentations were arranged to emphasize recent advances in our understanding of the anatomy and physiology of the NVU (Lo), recent studies on the astrocytes (Nedergaard), and pericytes (Fisher). The final 2 presentations describe the role of extracellular matrix enzymes in amyloid metabolism as it relates to Alzheimer disease (Lee) and vascular cognitive impairment (Rosenberg). The goal of the session was to provide an overview on the role of the separate cell types composing the NVU and to show how they interact in acute and chronic cerebrovascular diseases.

Transgenic mice have been used to explore the role of individual molecules in the function of the NVU. These studies are revealing roles for astrocytes and pericytes that have greatly added to our understanding while at the same time expanding the complexity. New methods of carrying these observations into the human with functional imaging of the blood–brain barrier (BBB) have also been developed. There is new information emerging on the role of the NVU in chronic degenerative diseases such as Huntington disease and amyotrophic lateral sclerosis.

Astrocytes play a critical role in the NVU. Recent studies on the mechanism of injury in Huntington disease indicate that the abnormal accumulation of protein in astrocytes may be important in cell death. Huntingtin is an important genetic factor for Huntington disease, and it can be found both in neurons and in astrocytic nuclei where it may interfere with glutamate transport. This recent evidence suggests that huntingtin in glial cells contributes to neuronal dysfunction and excitotoxicity in Huntington disease brains. Similarly, the superoxide dismutase model of amyotrophic lateral sclerosis may involve the NVU. Superoxide dismutase mutant mice have loss of tight junction proteins that precede motor neuron degeneration and neuroinflammation.

Many new methods have been developed to follow activity in a single cell or a small group of cells, including the recording of calcium transients both electrically and with optical methods. Astrocytes are numerous in the brain and maintain the microenvironment of neurons. They metabolize glutamate for consumption by the neuron and signal to each other through calcium mechanisms. An important feature of the astrocyte signaling mechanism is the reliance on ATP and involvement of glutamate. Death of astrocytes proceeds more slowly than that of neurons. Is it possible that therapies to preserve astrocytes may be more rewarding than attempts at treating neuronal death directly?

The pericyte has multiple roles in the function of the NVU. It is a unique cell with both macrophage and smooth muscle properties. Pericytes are less well understood because of the problems involved in immunostaining them. Finding a marker that differentiates the pericyte from other macrophages and from microglia would greatly help. There are several new antibodies that show selectivity for the pericyte that may clarify its role. Disruption of the NVU is related to substances released during inflammation by the pericytes. This includes cytokines, free radicals, and proteases, supporting a role similar to microglia/macrophages in neuroinflammation. Pericytes contain matrix metalloproteinase-3 (MMP-3); mice lacking the MMP-3 gene have an attenuated inflammatory response and fewer infiltrating neutrophils.

More recently, it has been suggested that pericytes may also possess properties of stem cells. If they are truly pluripotent, they probably play many roles that are critical for cellular function. They lie next to the endothelial cells in...
the region of the tight junctions where they could influence permeability. Their putative stem cell function suggests that they may have a role in the angiogenesis after brain injury. Newer staining methods should provide much-needed information about pericytes.

The link between amyloid and blood vessel disease is being explored with transgenic animals that overexpress a form of amyloid that accumulates in the blood vessels. Much confusion has surrounded research on amyloid because of the multiple forms and the different sites of pathology. Studies from many investigators are beginning to unravel the complexity. Aβ has a 40 and 42 amino acid form. Aβ(1–40) is the main one found in cerebral amyloid angiopathy and it interferes with the function of the blood vessel. Aβ(1–42) is more likely to accumulate in plaques in the insoluble fibrillary form created by combined action of a β-secretase and a γ-secretase rather than the normal formation of the soluble form of amyloid by degradation with an α-secretase. Not only is the formation of the amyloid products critical in determining the type of pathology, but the clearance mechanisms play a role. Stimulation of MMP-9 in the inflammatory cells by amyloid products affects the clearance rate by creating fragments that are more readily transported out of the brain. Because secretases may be inhibited by MMP inhibition, the design of drugs that reduce production may interfere with removal of the amyloid, which will complicate rational drug design of secretase and MMP inhibitors.

Emerging evidence suggests that an inflammatory process that damages the BBB is important in white matter damage in vascular cognitive impairment of the Binswanger type. Pathological studies show macrophages around blood vessels in regions of demyelination. The macrophages most likely are involved in the remodeling of a damaged blood vessel that has been exposed to chronic hypertension or diabetes. These inflammatory cells secrete free radicals and proteases. Pathological studies show MMP-2 in astrocytes and MMP-3 in inflammatory cells by amyloid products affects the clearance rate by creating fragments that are more readily transported out of the brain. Because secretases may be inhibited by MMP inhibition, the design of drugs that reduce production may interfere with removal of the amyloid, which will complicate rational drug design of secretase and MMP inhibitors.

In summary, there are improvements in ways to study the NVU in living cells and with transgenic animals with selective loss of a component of the BBB or a product that interferes with function of one or more components. In addition, more information on the role of the NVU in disease states is emerging from studies in transgenic animals and in human studies. This rapid increase in knowledge of the NVU provides insights that may eventually be translated into novel therapies.

Disclosures

None.

References

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Stroke. 2009;40:S2-S3; originally published online December 8, 2008;
doi: 10.1161/STROKEAHA.108.534404
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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