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Injury and repair in the neurovascular unit

Changhong Xing, Kazuhide Hayakawa, Josephine Lok, Ken Arai, and Eng H. Lo

Neuroprotection Research Laboratory, Massachusetts General Hospital, and Program in Neuroscience, Harvard Medical School, Boston, USA

Abstract

The neurovascular unit provides a conceptual framework for investigating the pathophysiology of how brain cells die after stroke, brain injury, and neurodegeneration. Emerging data now suggest that this concept can be further extended. Cell–cell signaling between neuronal, glial, and vascular elements in the brain not only mediates the mechanisms of acute injury. But integrated responses in these same elements may also be required for recovery as the entire neurovascular unit attempts to reorganize and remodel. Understanding the common signals and substrates of this transition between acute injury and delayed repair in the neurovascular unit may reveal useful paradigms for augmenting neuronal, glial, and vascular plasticity in damaged and diseased brain.

Keywords

Neuron; Astrocyte; Pericyte; Microglia; Endothelium; Plasticity; Stroke; Traumatic brain injury; Neurodegeneration

Introduction

The importance of cell–cell signaling between all elements of the neurovascular unit in stroke, brain injury, and neurodegeneration has been extensively discussed.^{1–4} Dysfunctional crosstalk between neurons, glia, and vascular compartments contributes to multiple aspects of acute pathophysiology in central nervous system (CNS) disease. Impaired glutamate release–reuptake mechanisms in neurons and astrocytes can amplify excitotoxicity.⁵ Perturbed signaling between cerebral endothelium, astrocytes, and pericytes can disrupt blood–brain barrier (BBB) integrity.⁶ Dysfunctional coupling between neuronal activation and vascular responses can promote deleterious spreading depression.⁷ And ultimately, disordered signaling between all neurovascular and gliovascular elements can underlie the evolution of neuroinflammation and cell death.⁸ By understanding how these complex multicellular events unfold, we may be able to move beyond a singular focus on ‘preventing neuron death’ towards a more integrative approach where we attempt to rescue function within and signaling between all cell types in the entire neurovascular unit.

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Correspondence to: E. H. Lo, MGH East 149-2401, Charlestown, MA 02129, USA. Lo@helix.mgh.harvard.edu.

Some concepts discussed here are based in part on data and ideas presented in previous reviews (Lok *et al.*, *Neurochem Res.* 2007; Lo, Br J Pharmacol. 2008; Lo, *Nat Med.* 2008; Arai *et al.*, *FEBS J.* 2009; Hayakawa *et al.*, *Ann New York Acad Sci.* 2010; Lo, *Nat Med.* 2010; Moskowitz *et al.*, *Neuron.* 2010).

To date, the neurovascular unit has been mostly applied as a conceptual tool to guide the investigation into acute mechanisms of injury. More recently, it is recognized that embedded within the acute pathophysiology of CNS disease, is the endogenous response of damaged brain itself.⁹ The evolution of brain injury and neurodegeneration comprises a dynamic balance and imbalance between initial triggers of injury and evolutionarily conserved responses of brain plasticity, remodeling, and compensation.¹⁰ The processes of acute injury and of long-term recovery are likely to involve analogous cell–cell signaling pathways, along with non-cell-autonomous mechanisms in the brain. In this short opinion piece, we briefly outline the principles of this idea and discuss recent data that may help us find common mechanisms of injury and repair in the neurovascular unit (Fig. 1).

Cell–Cell Interactions for Remodeling

One of the best early examples of cell–cell signaling in the neurovascular unit may be found in the original observations of the so-called neurovascular niche for neurogenesis. For decades, the standard model proclaimed that adult mammalian brains did not grow new neurons. But this paradigm was overturned when it was discovered that even in adult brains (at least in rodents), there existed pockets of ongoing neurogenesis, for example, in the subventricular zone next to the lateral ventricles and the dentate regions within the hippocampus. A closer examination of these neurogenic pockets revealed that neuroblasts always seemed to be closely associated with active microvessels, suggesting that endothelial–neuroblast crosstalk may exist.¹¹ Indeed, it has now been shown that coculturing neuroblasts with brain endothelium significantly promoted neurogenesis.¹² Of course, whether these primarily rodent phenomena persist in higher human brains remains to be determined.^{13,14}

From an evolutionary perspective, the underlying molecular mediators of neurogenesis and angiogenesis overlap and are highly conserved.¹⁵ Hence, after stroke and trauma, neurogenesis and angiogenesis appear to be tightly coregulated, especially during the recovery phase post-injury. Migrating neuroblasts move along perivascular pathways.¹⁶ Promoting neurogenesis seems to augment angiogenesis and *vice versa*.^{17,18} Some of these interdependent mechanisms may involve growth factors such as brain-derived neurotrophic factor (BDNF).¹⁹ Since growth factors not only promote cell growth, but also cell survival, it becomes increasingly clear that the cerebral endothelium may not just comprise ‘empty pipes’ for blood flow. Instead, they may represent an intricate endocrine organ embedded within the brain itself, supporting neuronal function and defending the brain parenchyma against neurotoxicity.^{20,21}

Another example of multicellular crosstalk in the neurovascular unit involves the interactions between the brain microvessel and surrounding astrocytes and pericytes. Developmentally, maturation of the BBB requires the coordinated development of adjacent glial cells.⁶ During brain injury or neurodegeneration, signaling between astrocytes, pericytes and endothelium become disrupted. Hence, repairing the leaking barrier entails restoring function in the entire gliovascular system including crosstalk between astrocytes and pericytes.²²

Plastic crosstalk can also be found between neurons and astrocytes. Release–reuptake of neurotransmitters is essential for brain function, and loss of proper communication between neurons and astrocytes exacerbates excitotoxicity. During remodeling of damaged or diseased neuronal circuits, crosstalk mechanisms may play especially critical roles. Astrocytes are known to release thrombospondin-1 which is a major regulator of synaptic maturation.²³ Reactive astrocytes also release tissue plasminogen activator, which may be required for recovering neurons to remodel their dendritic arbors.²⁴ Indeed, several studies have suggested that the therapeutic benefits of stem cell therapies may depend in part on the ability of astrocytes to amplify the effects on neuronal remodeling.²⁵ Mining the astrocyte secretome for novel mediators of neuroplasticity may be an important direction for future research.

Interactions between neurons, glia, and endothelium underlie the ability of the cortex to recover from injury and disease. However, for the large human brain, what happens in white matter may be even more important. Emerging data now suggest that besides a neurovascular niche, an analogous oligovascular niche may also exist. Astrocytes and cerebral endothelial cells secrete many trophic factors that support oligodendrocyte precursor cells.^{26,27} And after injury, vascular endothelial growth factor (VEGF)-mediated endothelial recovery is linked with the proliferation and migration of oligodendrocyte precursor cells.^{28,29} Oligodendrogenesis and angiogenesis are intricately linked.³⁰ Without proper remodeling in white matter, the recovering brain cannot reconnect.

Finally, accumulating data is beginning to suggest that non-cell-autonomous mechanisms may extend beyond the narrow confines of the CNS itself. Interactions between the blood/immune system and CNS underlies not just stroke and trauma,⁸ but also neurodegeneration.³¹ After focal strokes, alterations in a broad range of genes are readily detected in circulating blood cells.³² Beyond the obvious implications for biomarkers, systemic blood responses may also have therapeutic implications. A recent study provided proof of principle — oral administration of drugs that modify tryptophan metabolism in blood significantly ameliorated synaptic loss and functional deterioration in mouse models of Alzheimer's and Huntington's disease.³³ Hence, contrary to traditional assumptions, the CNS is not isolated from the rest of the body. Crosstalk between multiple cell types in the CNS and non-CNS are likely to be exceedingly complex. In the end, a systems biology approach may be required to truly dissect the mechanisms involved.³⁴

Biphasic Mechanisms in Injury and Repair

The biphasic nature of many mediators in neurobiology is well known. For example, trophic factors such as nerve growth factor and BDNF promote cellular survival via their primary receptors TrkA and TrkB respectively. But in contrast to these neuroprotective effects, both factors can also be neurotoxic via overactivation of the p75NTR receptor.³⁵ Within the context of the remodeling neurovascular unit, similar biphasic properties of many other factors and mediators may also emerge.

One of the most studied targets in neuroprotection may be the NMDA-type glutamate receptor. Over-activation of the NMDA receptor clearly induces acute excitotoxicity and

neuronal death in many animal models of cerebral ischemia, brain trauma, and neurodegeneration.⁵ However, in the delayed phase after injury and disease, these same NMDA signals may be required for recovery. Without NMDA signaling, neuroplasticity and repair of neuronal circuitry cannot take place. Beneficial NMDA mechanisms may involve augmentation of protective CREB signaling in neurons.³⁶ NMDA signaling may also promote the endogenous neurogenesis that occurs after brain injury.³⁷ Indeed, this may be where crosstalk in the neurovascular unit is manifested. A recent study suggests that neuroblast migration along the rostral migratory stream is dependent on proper communication between glutamate released from neuroblasts and NMDA receptors present on guiding astrocytic sheaths.³⁸

Another example of the biphasic nature of mediators in the neurovascular unit involves neurovascular proteases from the matrix metalloproteinase (MMP) family. Dysregulated MMPs are clearly detrimental. By degrading neurovascular matrix, MMPs damage the BBB and cause edema, hemorrhage, and neuronal death.³⁹ Knockout of MMP genes or inhibition with selected drugs all prove significantly protective in animal models of stroke and brain trauma. Indeed, a large body of experimental data has led to the initiation of clinical stroke trials testing minocycline as an MMP inhibitor.⁴⁰ Recently, however, a new aspect of MMP functioning has become apparent. Whereas MMPs disrupt neurovascular matrix and cause injury during acute stroke, they can promote neurovascular remodeling in peri-infarct cortex during the delayed stages of stroke recovery.⁴¹ MMPs also mediate the movement of neuroblasts during the endogenous neurogenic response that is triggered after brain injury.⁴² Whereas inhibition of MMPs during the first few hours after stroke reduces infarction, the same inhibitors worsen outcomes when applied several days later.⁴³

The idea of biphasic mediators is not restricted to acute brain injury per se. Similar patterns may be observed in 'slower' diseases of neurodegeneration. A good example may perhaps be found in the pleiotropic actions of amyloid-beta. In Alzheimer's disease, hippocampal degeneration is often accompanied by a reorganization of cholinergic networks from the basal forebrain.⁴⁴ From a functional perspective, plasticity in frontal regions and remapping of associated cortical networks may help the brain cognitively compensate for degenerating neurons.⁴⁵⁻⁴⁷ But how does this happen? Of course, amyloid overload is a key step in plaque formation and generation of toxic oligomers.⁴⁸ However, it has also been proposed that homeostatic levels of amyloid may help regulate transmitter release and synaptic function.^{49,50} Ultimately, the balance between beneficial-adaptive versus aberrant-maladaptive forms of synaptic and neuronal remodeling may significantly influence how disease evolves in Alzheimer brains.⁵¹

Reactive gliosis is a seminal feature of damaged or diseased brain. Traditionally, the glial scar is thought to be detrimental. Reactive glia secrete many inhibitory substrates that retard axonal and dendritic regrowth.⁵² Thus, antibody blockade of NOGO improved recovery in mouse models of focal stroke and brain injury.⁵³ Protease-mediated digestion of chondroitin sulfate proteoglycans enhanced functional recovery after stroke and CNS trauma.⁵⁴ Peptide inhibitors of semaphorins reconnected axons in a mouse model of spinal cord injury.⁵⁵ More recently, however, a more nuanced view of the reactive astrocyte has emerged. Reactive astrocytes can also release many trophic factors, such as nerve growth factor, basic

fibroblast growth factor, platelet-derived growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, Neuropilin-1, vascular endothelial growth factor, and others.^{52,56,57} Many of these trophic factors may be beneficial by promoting neuronal survival and augmenting coordinated responses in synaptogenesis, neurogenesis, and angiogenesis.^{58,59} Proof of concept can be obtained by suppressing these reactive astrocytes. For example, preventing reactive astrocytes from releasing the damage-associated molecular pattern mediator called HMGB1 results in worsened recovery after focal cerebral ischemia in mice.^{60,61}

The other major class of reactive glia in the CNS comprise the microglia. Microglia are resident immune cells of the CNS and serve as sensors and effectors in the normal and pathologic brain.^{62,63} Microglia have important homeostatic roles in normal brain. For example, microglia contribute to synapse remodeling and neurogenesis,^{64–67} and they can also be involved in blood vessel formation.⁶⁸ But after injury or disease, the role of microglia become even more complex. After an ischemic lesion, resident microglia are activated and accumulate within minutes of ischemia onset.⁶⁹ Post-ischemic microglia can be highly neurotoxic by producing damaging cytokines, reactive oxygen and nitrogen species, and extracellular proteases such as MMPs.^{70,71} However, it is now recognized that microglial activation is not a univalent state. Activated microglia can exhibit phenotypic and functional diversity. At least two activated phenotypes have been described: the classically activated M1 or the alternatively activated M2. Inflammatory M1 microglia release high deleterious levels of tumor-necrosis factor- α , IL-1 β , reactive oxygen species, and nitric oxide. In contrast, the M2 microglia produce much lower levels of nitric oxide, and higher levels of anti-inflammatory cytokines and neurotrophic factors, such as glial cell line-derived neurotrophic factor, BDNF, basic fibroblast growth factor, insulin-like growth factor 1, transforming growth factor- β , and VEGF.^{65,72–75} These types of microglia can be neuroprotective, help clear toxic byproducts of tissue damage, and promote neurogenesis and neuroplasticity. Because microglia possess both beneficial and harmful properties, optimal timing of microglia-based interventions relative to disease onset and progression will be necessary for therapeutic gain.

In theory, if one can distinguish the differential signaling mechanisms of detrimental versus beneficial CNS responses, one may design combination therapies to protect and repair the neurovascular unit. One example can be found in biphasic endothelial reactions to injury in the brain. In order to restorative angiogenesis to take place, endothelial cells will have to disengage and move. But in the process of disengaging, BBB integrity may be perturbed. VEGF is a potent angiogenic factor that induces endothelial cell proliferation, survival, migration, and invasion during development and in pathological conditions. However, VEGF also increases vascular permeability, and can lead to edema and extensive tissue injury in ischemic tissue after myocardial infarction or stroke.^{76,77} In animal models of stroke, early administration of VEGF (within 1 hour of onset) worsens outcome by increasing brain edema, whereas later administration (48 hours after onset) is beneficial.⁷⁸ Combination of angiopoietin-1 and VEGF or coexpression of angiopoietin-1 with VEGF increases BBB structural integrity and reduces edema and brain damage after ischemia, but does not affect the angiogenic effects of VEGF.^{79,80} Recent studies show that the Roundabout 4 (Robo4)–Slit2 signaling axis regulates vascular integrity by counteracting the

effects of VEGF, and suggests that Slit2 can both positively and negatively regulate angiogenesis by binding to Robo1 and Robo4, respectively.⁸¹ Activation of Robo4 blocks VEGF signaling and VEGF-induced angiogenesis and vascular permeability. Further dissection of this pathway may lead to novel ways of optimizing neurovascular protection and repair within the VEGF domain.⁸² Ultimately, any attempt to develop targeted therapies in brain injury and neurodegeneration must take into account the biphasic nature of all mediators in the remodeling neurovascular unit.

Conclusions

The concept of the neurovascular unit emphasizes that function and dysfunction in the CNS is not based on the neuron alone. All elements in neuronal, glial, and vascular compartments contribute to physiology and pathophysiology. In this brief opinion piece, we have attempted to extend this concept. Multiphasic and multicellular interactions between all these different cell types should also play a central role as the brain attempts to reorganize, compensate, and recover after stroke, trauma, and neurodegeneration (Fig. 1). In order to discover and optimize new therapies for neuroprotection and neurorepair, we will have to rigorously understand how plasticity within the entire neurovascular unit mediates the graded transition from initial injury into delayed remodeling.

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Figure 1.

Schematic of the multicellular interactions that mediate the transition from injury into repair in the neurovascular unit. During injury and disease, the BBB is leaky, inflammation is damaging, and neurotoxicity predominates. But during repair, endogenous mechanisms are activated that involve angiogenesis and neurogenesis, trophic glial reactions, and recruitment of beneficial aspects of inflammation and remodeling. In this simplified schematic, we only depict neurons, astrocytes, microglia and endothelium. Of course, recovery after CNS injury will also involve many other cell types including pericytes, smooth muscle cells, oligodendrocytes, infiltrating or resident immune cells as well as systemic responses in other organs. Ultimately, cell–cell signaling between all elements of the neurovascular unit is required to support neural plasticity and functional compensation and recovery.