MINIREVIEW

The Translational Significance of the Neurovascular Unit*

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The mammalian brain is supplied with blood by specialized vasculature that is structurally and functionally distinct from that of the periphery. A defining feature of this vasculature is a physical blood-brain barrier (BBB). The BBB separates blood components from the brain microenvironment, regulating the entry and exit of ions, nutrients, macromolecules, and energy metabolites. Over the last two decades, physiological studies of cerebral blood flow dynamics have demonstrated that substantial intercellular communication occurs between cells of the vasculature and the neurons and glia that abut the vasculature. These findings suggest that the BBB does not function independently, but as a module within the greater context of a multicellular neurovascular unit (NVU) that includes neurons, astrocytes, pericytes, and microglia as well as the blood vessels themselves. Here, we describe the roles of these NVU components as well as how they act in concert to modify cerebrovascular function and permeability in health and in select diseases.

NVU Components and Functions

The neurovascular unit (NVU) enables tight regulation of blood flow through the vasculature, which has unique structure in the brain. The arteries that dive into the brain from the subarachnoid space consist of endothelial cells (ECs), a basement membrane, smooth muscle cells, the perivascular (Virchow-Robin) space, pia mater, and astrocyte endfeet (see Figs. 1 and 2). As vessels continue deeper into the brain, they lose their smooth muscle cell and pia mater coverage, gaining pericytes between the EC and astrocyte endfeet. Along the length of the cerebral vasculature, neuronal and astrocyte processes contact other components of the NVU, where they can influence the function of the entire unit. Here we describe individual NVU components and their roles within the NVU.

Vascular Endothelial Cells

The ECs lining cerebral blood vessels are the core anatomical unit of the vascular blood-brain barrier (BBB), protecting the brain from systemic influences by limiting transcellular and paracellular transport mechanisms. Brain vascular ECs contain no fenestrae and undergo very low rates of transcytosis (1). Tight junctions (TJs) and adherens junctions formed between adjacent ECs underlie the physical barrier that impedes paracellular diffusion of ions, macromolecules, and other polar solutes (Fig. 1, A and B). Structurally, TJs are composed of combinations of integral membrane proteins including occludins and claudins (which form dimers with their counterparts on adjacent ECs) and cytoplasmic proteins that couple these transmembrane proteins to the actin cytoskeleton (2). The result is a tight interendothelial seal with in vivo transendothelial electrical resistances of up to 1800 ohms/cm² (3). In addition to a physical barrier, brain vascular ECs form a selective transport interface between the blood and the brain, similar to that of many epithelial surfaces throughout the body. The luminal and abluminal membranes of brain vascular ECs have polarized expression of transporters, metabolite-degrading enzymes, receptors, ion channels, and ion transporters (4), ensuring that nutrients such as glucose, amino acids, nucleosides, and electrolytes are delivered to the brain from the blood and that solutes and metabolite waste products are effluxed from the brain to the blood (2). The specialization of brain vascular ECs reflects the unique requirements of an organ that demands a homeostatic ionic environment and protection from neuroactive blood-borne solutes.

Pericytes

Pericytes are mural cells embedded within the basement membrane that envelopes blood vessels. Pericytes extend thin processes around and along pre-capillary arterioles, capillaries, and post-capillary venules (Fig. 1, A and B) (5). Their morphology varies with their position along the vascular bed, reflecting the existence of subpopulations with diverse functions in blood vessel formation, vessel maintenance and permeability, angiogenesis, clearance of cellular debris, immune cell entry, and cerebral blood flow (CBF) regulation (5–7). As a member of the NVU, pericytes are able to communicate directly with cerebral ECs through gap junctions and with other pericytes via peg-and-socket contacts (8, 9). The importance of pericytes in the NVU is further illustrated in development, during which pericytes induce polarization of astroglial endfeet around vessels, and in disease, in which pericyte degeneration leads to increased vessel permeability (10). Pericytes have even been shown to have stem cell-like properties, making them capable of potentially differentiating into other cell types found in the NVU (11, 12).

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2 The abbreviations used are: NVU, neurovascular unit; EC, endothelial cell; BBB, blood-brain barrier; TJ, tight junction; CBF, cerebral blood flow; ECM, extracellular matrix; AA, arachidonic acid; 20-HETE, 20hydroxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; AD, Alzheimer’s disease; APP, amyloid precursor protein; Aβ, amyloid β.

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Astrocytes

Classically, astrocytes have been considered the physical, biochemical, and metabolic support cells of the CNS. Astrocytes are distributed throughout the brain and exhibit heterogeneous, star-shaped, highly branched morphology that varies with their location and, more specifically, on the cell populations with which they interact. Individual astrocytes can extend processes to several neurons and synapses and also extend foot-like processes that encase cerebral vessels. Astrocytes are therefore ideally localized to sense and respond to both neuronal and vascular activity. Individual astrocytes occupy their own non-overlapping spatial domain, they are interconnected with neighboring astrocytes by gap junctions to facilitate long-range signaling (14). In the context of the NVU, astrocytes are centrally positioned between neurons and ECs, which allows them to respond dynamically to synaptic activity and neuronal metabolism to help regulate CBF. Astrocytes extend endfoot processes to the surface of cerebral blood vessels, providing ~99% abluminal vessel coverage (15, 16). Endfeet express high levels of aquaporin-4 water channel proteins, which are thought to be critical for perivascular clearance mechanisms via the newly characterized glymphatic system (Fig. 2) (17). Developmentally, secretion of growth factors from astrocyte endfeet induces TJ formation and up-regulates transport system proteins in vascular ECs (18). During adulthood, bidirectional signaling between astrocyte endfeet and brain ECs helps maintain vascular integrity (19–21).

Neurons

In the brain, neuronal processes are in physical contact with the vasculature, and these associations mediate a local increase in CBF in response to increased neuronal metabolic demand at that location, a mechanism known as functional hyperemia (see under “Functional Hyperemia”). In brief, vasoconstriction and dilation are thought to be driven by the contractility of arteriolar smooth muscle cells and capillary pericytes responding to release of neuron- and astrocyte-derived vasoactive substances including COX-2-derived prostanoids (22), nitric oxide (23), vasoactive intestinal polypeptide (24), acetylcholine (25), corticotropin-releasing factor (26), neuropeptide Y (27), and somatostatin (28). Regional regulation of CBF by neurons appears to be a complex function of: 1) the developmental stage of the brain, 2) the brain region and the populations of neurons served by the vasculature, 3) the presence and nature of glial cells that may serve as local mediators of neuronal stimuli, 4) the duration and magnitude of neuronal activity, and 5) the effects of

FIGURE 1. Anatomical structure of the NVU. A, a schematic representation of a capillary cross-section within a single neurovascular unit demonstrates the following important features: 1) Specialized brain endothelial cells line cerebral vessels. 2) Tight junctions between endothelial cells restrict paracellular diffusion and effectively “seal” the vessels. 3) A continuous basal lamina/basement membrane encases endothelial cells. Pericytes are embedded within this matrix, situated between endothelial cells and astroglial endfeet. 4) Astrocytes are centrally positioned within the brain parenchyma. These cells extend processes that communicate with local neurons and synapses and also extend foot-like processes that encase cerebral vessels. Astrocytes are therefore ideally localized to sense and respond to both neuronal and vascular activity. 5) Resident microglia use long cellular processes to survey their microenvironment and can quickly respond to insults at or near the NVU. 6) Local interneurons innervate cerebral vasculature and can induce vessels to change their tone based on incoming neuronal afferent signals (28) (adapted with permission from Macmillan Publishers Ltd.: Abbott et al. (2006) Nat. Rev. Neurosci. 7, 41–53 (97), © Macmillan Publishers Ltd.). B, electron micrograph of a capillary cross-section in rat brain. C, 3D reconstruction of immunofluorescent NVU images taken on a confocal microscope demonstrating von Willebrand Factor reactivity (endothelial cells) and glial fibrillary acidic protein reactivity (astrocytes) outside the vascular wall (panels B and C reprinted from Weiss et al. (2009) Biochim. Biophys. Acta 1788, 842–857 (98), with permission from Elsevier, © Elsevier).
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brain injury or disease that may alter any of these other factors. The association of neuronal processes with cerebral vasculature is also important for the development and maintenance of the BBB. During development, vascular endothelial growth factor (VEGF) signaling appears to drive vascular patterning (29); however, neural progenitor cells contribute to the stabilization of the nascent network (30). Post-developmen tally, it is likely that neuronal activity continues to participate in the maintenance of the vascular network (31), with astrocytes, rather than neurons, as the chief mediators of cerebrovascular permeability.

**Basement Membranes**

Secreted proteins make up a specialized extracellular matrix (ECM) that forms the basement membrane between ECs and pericytes and between astrocytes and pericytes (Fig. 1A). Pericyte coverage of vasculature is discontinuous; in areas of discontinuity, a single basement membrane is shared between astrocytes and ECs. Proteomic studies from rodent vasculature demonstrate that the brain vasculature ECM protein composition differs from that present in the periphery. Even within the brain, basement membrane protein composition varies greatly between large and small vessels (32), providing evidence that the NVU is functionally heterogeneous throughout the brain. Key proteins of the basement membranes include numerous isoforms of ECM proteins such as collagens, fibrillins, laminins, vitronectin, and fibronectin as well as soluble factors (e.g. growth factors and cytokines), enzymes responsible for matrix degradation and processing (including matrix metallopro teases), and proteins known to bind to ECM (e.g. lectins and semaphorins). Both ECM and support protein components of the basement membrane are essential to proper NVU functioning as they directly mediate the activation state of many receptors on the cellular components of this unit. Dysfunction and degradation of the basement membrane are associated with several CNS disease states.

**Microglia and Perivascular Macrophages**

Microglia are the primary immune cells of the brain. Early in development, these yolk sac-derived myeloid precursors seed the brain (33, 34), where they develop into highly plastic cells with motile capabilities. During their native resting state, microglia have small cell bodies with numerous long and highly branching processes (Fig. 1A). Under pathologic conditions, microglia become activated and take on an amoeboid morphology (larger nuclei and cell bodies with shorter processes), produce and secrete numerous cytokines and soluble factors, and become highly phagocytic (35). The activation state of microglia is often considered polarized as an M1 or M2 phenotype, with the cells diverging to either pro-inflammatory or anti-inflammatory functions, respectively, based on altered expression of cell membrane receptors and secretable factors. However, in vivo, there is a wide range of microglial activation phenotypes that reflect the specific insult administered and the state of the surrounding NVU cells. Current research is investigating novel strategies to modulate microglial polarization as a potential therapeutic target (36, 37).

Perivascular microglia/macrophages that originate from both CNS-resident microglia and bone marrow-derived circulating monocytes also exist in the NVU (33, 38). During development, vasculature-associated microglia interact with tip cells on sprouting vessels to facilitate angiogenesis. In the adult brain, perivascular macrophages are likely derived from and replenished by circulating monocytes, and act as a first line of defense against invading pathogens (39). Perivascular macrophages maintain contact with the other cell types of the NVU, and crosstalk between these cells likely contributes to NVU function and dysfunction. Recent studies employing intravital two-photon microscopy reveal that in several pathological states, parenchymal microglia can migrate to form perivascular cuffs, leading to vascular degradation and disease progression (40–42). In contrast, perivascular macrophage phagocytosis is hypothesized to clear neurotoxic substances in Alzheimer’s disease (AD; see under “Alzheimer’s Disease”) (101).

**NVU: Intercellular Interactions**

Interactions occur between neural, glial, and vascular components of the NVU in response to physiological stimuli, facilitating activity-dependent regulation of vascular permeability,
CBF regulation, and neuroimmune responses. On the whole, these interactions maintain CNS homeostasis. To illustrate this, we highlight their influence on CBF, focusing on mechanisms of functional hyperemia.

**Functional Hyperemia**

Cerebral circulation can be regionally modified based on the energy demands of local neural tissue. Temporal and spatial orchestration of increased blood flow to CNS tissue in response to neural activity is termed functional hyperemia (1). To effect the delivery of blood substrates such as oxygen and glucose to metabolically active regions of the brain, local groups of neurons and their associated astrocytes signal to smooth muscle cells or pericytes and vascular ECs to modify vascular tone. Although neurons are able to contact and signal to the vasculature directly, astrocytes can act as relays between neurons and ECs (43).

In glutamate neurotransmitter-regulated neurovascular signaling, synaptic glutamate released during increased neuronal activity binds to NMDA receptors on nearby neurons and to metabotropic glutamate receptors on astrocytes. Glutamate binding results in intracellular calcium ([Ca$^{2+}$]) increases in both neurons and astrocytes, stimulating the release of vasoactive compounds (Fig. 3) (43, 44).

In astrocytes, the increased [Ca$^{2+}$]$_i$ activates phospholipase A$_2$ (PLA$_2$), which then produces arachidonic acid (AA). AA can be released at astrocyte endfeet to the contractile elements of vascular walls, where it is converted to its metabolite, 20-HETE, which elicits vasoconstriction. As astrocytic AA accumulates, it is also converted to the vasoactive metabolites prostaglandin and epoxygenocatrienoic acid (EET), which are released to elicit vasodilation (45, 46). Increases in [Ca$^{2+}$]$_i$ in astrocyte endfeet can also activate large-conductance calcium-gated potassium channels and stimulate K$^+$ efflux onto vessels, resulting in vasodilation (47, 48). The role of astrocyte [Ca$^{2+}$]$_i$ oscillations in neuronal-vascular coupling was demonstrated in experiments showing that blockade of neuronal activity-dependent [Ca$^{2+}$]$_i$, elevations within astrocytes impaired the ability of astrocytes to control arteriole tone (49). The specific vasomotor response elicited by increased astrocyte [Ca$^{2+}$]$_i$ depends on factors such as local oxygen concentrations and the pre-existing vascular tone (43, 50).

In neurons, increased [Ca$^{2+}$]$_i$, activates neuronal NOS, creating NO, which induces vasodilation through its action on cGMP in arteriolar smooth muscle cells and has been proposed to modulate astrocyte-vascular signaling pathways via inhibition of EET and 20-HETE (51). As in astrocytes, increased neuronal [Ca$^{2+}$]$_i$ activates PLA$_2$, producing AA. The vasoactive metabolites of AA are released to act on the contractile cells of vascular walls (1, 52). Neurons can also modulate neurovascular coupling by signaling directly to vascular smooth muscle cells and ECs. Additionally, numerous vasoactive mediators (acetylcholine, GABA, neuropeptide Y, somatostatin) released from neurons during neural activity have been shown to elicit vasomotor responses (Fig. 3) (28, 43, 53).

Although the relative contributions of astrocytes and neurons to vasomotor responses vary as a function of brain region and local neural anatomy, the vasoactive mediators released from both cell populations act together either synergistically or antagonistically to precisely regulate CBF within their microdomains (43). Taken together, these observations highlight the extensive communication that must occur between NVU components to match blood flow with regional activity levels.

**NVU: Pathology**

Disease can lead to aberrations in cellular communication between NVU constituents and result in impaired brain function. Here we discuss AD and CNS neoplasms, two pathologies with cerebrovascular dysfunction that demonstrate principles of NVU function.

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FIGURE 3. Neurovascular unit components act in concert to regulate cerebral blood flow. Glutamate is released during increased neuronal activity and binds receptors on astrocytes and neurons, inducing rises in intracellular calcium (Ca$^{2+}$) levels. Ca$^{2+}$ activates precursors that stimulate release of vasoactive mediators that induce cerebral vessels to contract or dilate after binding their vascular receptors. This concerted activity between neurovascular unit components allows precise regulation of vasomotor responses to effect delivery of oxygen and glucose to brain regions with increased neuronal activity (adapted with permission from Macmillan Publishers Ltd.: Attwell et al. 2010 Nature 468, 232–243 (43), © Macmillan Publishers Ltd.; and from The American Physiological Society: Hamel et al. (2006) (100) J. Appl. Physiol. 100, 1059–1064, © The American Physiological Society).
**Alzheimer’s Disease**

The marked cognitive decline seen in patients with AD is associated with neurovascular dysfunction (50) as manifested in impaired clearance of proteins that are widely believed to be toxic, most notably the amyloid β (Aβ) peptide. Aβ is aberrantly formed when the transmembrane receptor amyloid precursor protein (APP) is cleaved by β-secretases and γ-secretases to release soluble Aβ. Mutations in genes that either encode the APP substrate or encode proteins involved in its processing to Aβ uniformly produce dominantly inherited forms of AD, indicating the key role of this peptide in the pathogenesis of AD (52). Several isoforms of soluble Aβ monomers can be produced and exist in equilibrium with one another, with hypothesized neurotoxic effects; β-sheet-mediated interactions between these lead to progressive aggregation to form insoluble deposits. These are constituted in the cerebral cortex as amyloid plaques, one of the hallmark lesions of AD, but are also found in and around cerebral blood vessels.

Aβ can be cleared from the brain via enzymatic degradation, EC transport system-mediated clearance, or interstitial bulk flow and perivascular limbic clearance into cerebrospinal fluid (53). In sporadic late-onset AD in particular, Aβ accumulation is thought to be due to faulty clearance, rather than overproduction (53). Impaired clearance of Aβ across the cerebrovascular endothelium is believed to result in Aβ deposition in and around cerebral blood vessels, a condition known as cerebral amyloid angiopathy. This condition produces a structural weakening of the vasculature that predisposes affected patients to brain hemorrhage.

According to one hypothesis of AD, inflammatory signaling that increases with aging results in increased expression of APP, impairments in its secretion, and deficiencies in axonal transport that depend on microtubules (54); APP and its Aβ cleavage products accumulate in swollen axonal compartments that become leaky due to microtubular failure and resulting transport deficiencies. Aβ cleavage products are eventually extruded through the leaky axonal membranes into the brain interstitial fluid, where they can be taken up and degraded by nearby neurons (55). Alternatively, Aβ will persist in the brain interstitial space and form amyloid plaques (54).

Extruded Aβ can also be taken up by glial cells. Although microglia are spatially associated with neuritic amyloid plaques containing dystrophic axons and dendrites, microglial ablation in two different mouse models of AD did not affect Aβ deposition (56). Although microglia do phagocytose aggregated and misfolded Aβ (57), they later extrude it (58), and proponents of the inflammation hypothesis of AD contend that this uptake may be a byproduct of the increased microglial clearance stimulated by nearby degenerating neurites (56). As the disease becomes chronic, senescent microglia that are thought to become hyperreactive initially may demonstrate decreased responsiveness to damage signals over time, allowing peptides and debris to accumulate locally, perhaps creating a “hot spot” that is permissive for plaque formation (54).

The role of astrocytes in AD pathophysiology is poorly characterized. Although some studies have demonstrated that astrocytes take up and degrade Aβ, others have shown that astrocytes actually produce and secrete high levels of it. As in the case of microglia, these seemingly contradictory findings may reflect different astroglial activation states. Astrocytes may take up and degrade Aβ in relatively newly formed senile plaques (59), but this may decline as AD progresses, perhaps as local cytokines and Aβ itself activate astrocytes to produce and secrete Aβ in a feed-forward mechanism (60, 61). Importantly, changes in astrocytes in AD have been linked with the development of perivascular Aβ deposits (62) and are likely to have more widespread consequences as astrocytes fail to survey and occupy their territorial domains.

**Neoplastic Disease**

Another example of cerebrovascular dysfunction may be found in CNS neoplasms, including both primary (tumors originating within the CNS) and secondary (metastatic) tumors. In both conditions, neoplastic cells early in disease can survive within the perivascular space of the NVU and later remodel, destroy, and produce new vasculature with aberrant NVU components and function (63). Understanding the NVU in neoplastic disease will open up novel treatment strategies, as this specific niche is critical for tumor development and drug delivery.

Gliomas, tumors arising from glial cells, provide an optimal example of NVU pathology in CNS malignancies. Glioma cells in the perivascular space can migrate within perivascular spaces and are in direct contact with the NVU basement membrane(s) and its associated soluble factors. These components promote glioma development by: 1) providing traction support for migration utilizing proteins such as collagen, fibronectin, and vitronectin, 2) promoting survival and proliferation, and maintaining multi-potency via activation of pathways including TGF-β, cytokine, notch, sonic hedgehog, and ECM signaling, and 3) facilitating radio- and chemotherapy resistance (64–69). Furthermore, glioma cells can produce and secrete additional ECM and growth factor proteins as well as matrix metalloproteinases to loosen the ECM for invasion (70). A delicate balance of cell adhesion for traction force coupled with ECM degradation for motility is necessary for successful infiltration. Glioma cells overexpress potentially targetable receptors, such as integrins, to mediate these processes.

In addition, complex molecular signaling and crosstalk between glioma cells and the cells of the NVU also dictate tumor survival and progression (71–74). These cell-cell interactions promote tumorigenic processes and disrupt normal NVU functions. Displacement of normal astrocyte endfeet promotes vascular “leakiness” through down-regulation of TJ expression (54) and disrupted regulation of vascular tone. Using acute slices and Ca2+, Watkins et al. (75) showed that perivascular glioma cells could even take over the regulation of vascular tone in a K+-dependent manner.

Beyond disrupting the NVU by individual or small clusters of neoplastic cells, larger tumors promote neovascularization to ensure adequate oxygen and metabolic support; these newly induced vessels have abnormal NVU structure and function (Fig. 4) (76). Glioblastoma cells release pro-angiogenic growth factors such as VEGF, which activates VEGF receptors on endothelial cells, inducing them to sprout and extend into the tumor (77, 78). Newly formed vessels can lack structural com-
components of the NVU, such as adequate pericyte coverage, normal EC walls and TJs, and normal basement membrane composition, and have variable permeability (79, 80). Understanding the increased, yet heterogeneous, permeability of tumor vasculature is essential for optimizing drug delivery to tumors. In clinical practice, CNS tumor vascularity is assessed by an MRI-derived parameter, $K_{\text{trans}}$, which reflects both vascular surface area and permeability. The role of VEGF in tumor-associated permeability can be seen in the decrease in $K_{\text{trans}}$ that occurs after treatment with the VEGF inhibitor, bevacizumab (Fig. 4D) (81).

**Future Directions**

Tremendous progress has been made in our understanding of the cellular contributions to the NVU; however, there is still much to learn about how the cellular players act in concert in health and disease to supply the brain. The discovery of glymphatic fluid flow (17) has led to consideration of new roles for all these players in a novel CNS clearance pathway that recapitulates functions of the peripheral lymphatic system that is missing in brain (Fig. 2) (82–84). How this clearance system is impaired in AD is an area of active research (53), but it also warrants exploration in other diseases (e.g., perivascular spaces as a key site of tumor progression (66, 69, 75) and tauopathies associated with impairment of lymphatic function after traumatic brain injury (85)) and for novel pharmacological targets. Lastly, because the perivascular space communicates with the cerebrospinal fluid space and dural lymphatics, which in turn drain into the deep cervical lymph nodes (82, 83), further study is needed to assess whether biomarkers such as exosomes, cytokines, or microRNAs in these compartments could provide insights into NVU pathology or novel diagnostic opportunities, and whether this clearance pathway plays a role in CNS pathological conditions such as communicating hydrocephalus (86, 87).

Drug delivery to the CNS remains a challenge. Countless dollars have been spent developing drugs that show promise in preclinical studies but fail to reach therapeutic levels in the brain in vivo. Improved targeting could be achieved by increasing access of agents to the NVU or decreasing their clearance. To improve drug delivery to the NVU, EC TJs can be transiently opened using a variety of methods to allow pharmacological agents to pass paracellularly between ECs. Alternatively, drugs can use receptor-mediated transport system routes through ECs. Drugs that are able to enter the NVU, but are rapidly cleared, could be maintained at therapeutic doses by blocking efflux pumps or inhibiting perivascular clearance routes.

**Recent Advances** in in vitro modeling systems, imaging technologies, and high throughput screening are providing cutting edge tools to allow advances in this area. Numerous ex vivo BBB models have been designed, frequently employing Transwell-style assays that include several of the cellular components of the NVU, and can be used to test drug delivery (88). Advanced imaging modalities, including super-resolution microscopy, live imaging using two-photon microscopy, improved transmission electron microscopy, and PET-MRI, can now be applied to study transport mechanisms in and out of the NVU from the nanoscale to whole brain. Technical advances have also paved the way for recent studies characterizing the transcriptomics and proteomics of the cerebral vasculature and surrounding cell types, resulting in large databases (recently reviewed in Ref. 89) that can inform research on specific proteins to be employed for drug transport. Combining these tools, recent reviews advocate for dual screening of molecules that interact with solute carriers on the cerebrovascular endothelium to traffic into the NVU, then using various methods to shuttle molecules across the vasculature by conjugating them
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to peptides and antibodies, or loading them into nanoparticles (90–92). Pioneering work in this field has demonstrated that use of the transferrin and insulin receptors can greatly enhance delivery to the CNS in rodent and nonhuman primate models (93, 94). These studies are now reaching clinical trials, an exciting landmark in targeted CNS therapeutics. Other groups are investigating inhibition of efflux mechanisms to maintain drug delivery in the NVU.

In summary, the NVU serves as the gateway to the brain. Understanding its components, development, maintenance, functions, and pathologic conditions will provide essential insights and tools needed to treat essentially all diseases that affect the brain.

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