Neurovascular signaling in the brain and the pathological consequences of hypertension

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Dunn KM, Nelson MT. Neurovascular signaling in the brain and the pathological consequences of hypertension. Am J Physiol Heart Circ Physiol 306: H1–H14, 2014. First published October 25, 2013; doi:10.1152/ajpheart.00364.2013.—The execution and maintenance of all brain functions are dependent on a continuous flow of blood to meet the metabolic needs of the tissue. To ensure the delivery of resources required for neural processing and the maintenance of neural homeostasis, the cerebral vasculature is elaborately and extensively regulated by signaling from neurons, glia, interneurons, and perivascular nerves. Hypertension is associated with impaired neurovascular regulation of the cerebral circulation and culminates in neurodegeneration and cognitive dysfunction. Here, we review the physiological processes of neurovascular signaling in the brain and discuss mechanisms of hypertensive neurovascular dysfunction.

¹astrocyte; cerebral blood flow; hypertension; neurovascular coupling; parenchymal arteriole

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The brain has a high basal metabolic rate and limited capacity to store energy. As a result, the execution and maintenance of all brain functions are dependent on a continuous flow of blood that is at all times and under all conditions sufficient to meet the metabolic needs of the tissue. The cerebral vasculature, as the infrastructure by which the brain receives the resources necessary to support neural processing and maintain the milieu necessary for neural homeostasis, is elaborately and extensively regulated by signaling from neurons, glia, interneurons, and perivascular nerves.

The brain is particularly vulnerable to hypertensive injury. Hypertension leads to neurodegeneration and cognitive disability and has been causally linked to dementia and Alzheimer’s disease (23, 64). It is increasingly evident that hypertensive neurodegeneration is a consequence of the damaging effects of high blood pressure on the cerebral vasculature. Chronic and even acute exposure to elevated intravascular pressure sets in motion a number of pathological mechanisms that disrupt the neurovascular regulation of cerebral blood flow (CBF). To understand how these mechanisms interfere with neurovascular signaling in the brain, the physiological mechanisms of these processes must first be understood. In this review, we provide an overview of neurovascular signaling in the brain and discuss mechanisms of hypertensive neurovascular dysfunction.

Neurovascular Regulation of CBF: Anatomy of the Cerebral Circulation

The cerebral vasculature consists of pial arteries located at the base and on the surface of the brain and their downstream tributaries. Pial arteries branch and narrow into pial arterioles, which also run along the brain surface. Pial arteries and arterioles are innervated by nerve fibers arising from the superior cervical, sphenopalatine/otic, and trigeminal ganglia (67). At various points, pial arteries and arterioles form perpendicular branches that dive from the surface parent artery into the brain parenchymal tissue, called “parenchymal arterioles” (also referred to as “penetrating arterioles”). The point of entry of the arteriole into the brain parenchyma is surrounded by a small, cerebrospinal fluid-filled pocket called the Virchow-Robin space. Innervation by extrinsic nerve fibers terminates at the Virchow-Robin space, beyond which parenchymal arterioles are directly contacted, or “innervated,” by glial and neuronal cell types. Parenchymal arterioles are predominantly surrounded by “endfoot” terminals of astrocyte projections, but there is evidence to suggest they are also contacted directly by interneurons (24, 173). Brain capillaries are enveloped by astrocytic endfeet as well, with pericytes occasionally intervened between the endfoot and capillary wall. The neurovascular regulation of CBF occurs primarily at pial arteries and parenchymal arterioles; however, neurovascular signaling through contractile pericytes has been suggested to regulate capillary diameter as well (53, 68).

Neurovascular Regulation of Pial Artery Tone by Extrinsic Perivascular Nerves

The sympathetic nerves arising from the superior cervical ganglion that innervate pial arteries and arterioles on the brain surface modulate vascular tone through the release of the contrac-
tile substances norepinephrine (NE) and neuropeptide Y (NPY) (45, 67). Parasympathetic nerve fibers from the sphenopalatine/otic ganglia innervating these vessels release the vasodilators acetylcholine (ACh), vasoactive intestinal peptide (VIP), and nitric oxide (NO), and fibers from the trigeminal ganglion release calcitonin gene-related peptide, substance P, and pituitary adenylate-cyclase activating polypeptide, to name a few (6, 45, 67). One role of vasoconstrictr release from sympathetic nerves is to shift the range of arterial blood pressures over which CBF remains relatively constant, or “autoregulates,” to higher pressures. (45). Parasympathetically released vasodilators restore resting tone after vasoconstriction and have been implicated in pathological conditions associated with vasodilation, such as migraine (176). For a thorough review of cerebrovascular regulation by extrinsic nerves, see Hamel (67).

Neurovascular Coupling: Matching CBF to Neuronal Activity

The major function of neurovascular signaling in the brain is to precisely coordinate perfusion in space and time to match the metabolic needs of the neurons. In most, if not all, tissues, an increase in cellular metabolism is accompanied by an increase in blood flow. When this occurs, it is known as functional hyperemia, a phenomenon in the brain that has been appreciated for well over a century and is vital for neural processing and viability (116, 142). The process by which functional hyperemia occurs in the brain, referred to as “neurovascular coupling” (NVC), involves the rapid communication to the cerebral vasculature of signals arising from active neurons. Upon receipt, these signals cause vasodilation and increase local CBF to a level sufficient to support and maintain neuronal function. The vascular targets for CBF regulation in NVC are parenchymal arterioles as well as pial arteries and arterioles. A role for pericyte regulation of capillary diameter in NVC has also been proposed (53, 68); however, the evidence supporting this role is limited.

NVC is studied in vivo by quantifying vascular diameter or hemodynamic responses to the activation of neurons by a sensory or electrical stimulus. Commonly, this is done in the retina by stimulation with light and in the cerebral cortex using contralateral whisker stimulation, fore-/hindlimb stimulation, or electrical stimulation of basal forebrain afferents. Insights into the molecular mechanisms underlying NVC have also been obtained by examination of the neurovascular unit (neurons, astrocytes, and microvessels) in brain slices by observing vascular responses to electrical depolarization of neurons or localized release of putative mediators induced by photolytic cleavage of molecular cages containing the compounds. Both in vivo and brain slice approaches are often used together to exploit their respective strengths and mitigate their individual weaknesses. In vivo experiments lack control over the extracellular environment and can be confounded by changes in circulating factors and the presence of various anesthetics. Brain slice experiments permit better optical resolution and the control of the extracellular milieu without confounding systemic effects, but the blood vessels are not subjected to physiologic flow or pressure. Collectively, these approaches have demonstrated that NVC is a multilayered, interactive process of extraordinary complexity that is intricately sculpted and finely tuned. Moreover, the mechanisms that mediate NVC may vary in a neuronal network-specific manner.

Astrocytes in NVC

Substantial evidence supports a role for astrocytes in NVC. Astrocytic endfeet, which wrap around parenchymal arterioles within the brain, are vasoregulatory centers that modulate vascular tone. Other projections (as many as 160,000) from astrocytes terminate at neuronal synapses, creating a “tripartite” synapse consisting of presynaptic and postsynaptic neurons and the astrocytic terminal (75). As a result of this configuration, astrocytes are positioned to monitor and modify synaptic activity. The current paradigm is that the engagement of neurons and consequent generation of action potentials result in the synaptic release of neurotransmitters that stimulate astrocytes to generate inositol 1,4,5-trisphosphate (IP3), initiating an IP3 receptor (IP3R)-dependent Ca2+ wave that propagates through the astrocyte to the perivascular endfoot (Fig. 1). It is generally thought that the astrocytic response to neuronal activity is mediated by glutamate binding to G protein-coupled group I metabotropic glutamate receptors (mGlurRs), mGluR5 and (to a lesser extent) mGluR1 (62, 136, 188). This view is consistent with the fact that these isoforms signal through Ga and trigger activation of the enzyme phospholipase C (PLC)-β to hydrolyze membrane phosphoinositides and generate IP3 (1, 12, 114, 169). In a recent study (160), it was reported that mGluR5 is expressed in astrocytes from young (<2 wk postnatal) but not adult mice. The authors of this study suggested instead that the predominant isoform in young mouse and human astrocytes is mGluR3, which negatively regulates the adenylate cyclase/cAMP/PKA pathway and has been linked to adenosine release and cGMP turnover (5, 115, 139, 182). Because mGluR3 agonists are not Gq-coupled and therefore presumably do not increase intracellular Ca2+ concentration ([Ca2+]i) in astrocytes, which experimental evidence suggests is a requirement for astrocyte-mediated vasoregulation (41, 62, 158, 159, 187), it is unlikely that mGluR3 directly mediates NVC, although it could conceivably modulate it. Ultimately, molecular evidence for developmental stage-dependent expression of mGluR5 must be weighed against clear functional evidence showing that type I mGluR agonists induce an increase in astrocyte Ca2+ and promote dilation of brain arterioles in adult mice (62, 136). Nevertheless, while the preponderance of evidence continues to support a central role for Gq-coupled mGlurRs in translating neuronal activity into an elevation in astrocytic endfoot Ca2+ and for astrocytic endfoot Ca2+ in controlling vascular diameter, recently raised questions about the developmental regulation of mGluR subtype expression (160) and the relative contribution of astrocyte Ca2+ signaling to NVC (126, 164) highlight the importance of continued research in this area. Other pathways through which neurotransmitters released by active neurons might mediate NVC by stimulating astrocytic Ca2+ signaling will be discussed below in Neurons in NVC.

Neuronally evoked astrocytic Ca2+ signals seem to be primarily mediated by IP3R-dependent endoplasmic reticulum (ER) Ca2+ release. In brain slices, flash photolysis of caged IP3 in astrocytic endfeet increases endfoot [Ca2+]i (158). More
Fig. 1. Neuronal network-specific mechanisms of neurovascular coupling. Signaling mechanisms engaged in the cortex to promote vasodilation and increase cerebral blood flow in response to activation of cholinergic basolocortical afferents via basal forebrain stimulation (A) or activation of glutamatergic thalamocortical afferents via somatosensory stimulation (B). Parenchymal arterioles are depicted at the right of each image. Blue, endothelial cell (EC); pink, smooth muscle cell (SMC); green, astrocyte (A); purple, pyramidal neuron; red, GABA inhibitory interneuron; yellow, vasoactive intestinal peptide (VIP)/choline acetyltransferase interneuron; orange, nitric oxide (NO) synthase/neuropeptide Y (NPy) interneuron; turquoise, somatostatin (SOM) interneuron. Neurotransmitters released from ascending afferent neurons are shown in blue for A and orange for B. Mediators derived from pyramidal neurons are shown in purple, interneurons in red, astrocytes in green, and vascular ECs in dark blue. R, receptor; mAChR, muscarinic Ach receptor; nAChR, nicotinic Ach receptor; mGluR, metabotropic Glu receptor; NMDA, N-methyl-d-aspartate; AMPA, α-amino-hydroxy-5-methyl-4-isoxazolepropionic acid; BK, large-conductance Ca2+-activated K+ channel; Kir, inward rectifier K+ channel; P2YR, P2Y receptor; EET, epoxyeicosatrienoic acid; EP, PGE2 receptor; COX, cyclooxygenase.
over, depletion of ER Ca$^{2+}$ stores with cyclopiazonic acid greatly attenuates (by 90%) the increase in astrocytic Ca$^{2+}$ induced by activating neurons with electrical field stimulation (EFS), whereas ryanodine does not, indicating that ryanodine receptor-mediated ER Ca$^{2+}$ release is not involved (158). With respect to Ca$^{2+}$ entry pathways, the L-type voltage-dependent Ca$^{2+}$ channel (VDCC) blocker nifedipine has been shown to reduce astrocytic endfoot [Ca$^{2+}$]$_i$ to EFS (55). This result likely reflects inhibition of VDCCs in cortical neurons and not in astrocytes (9, 31, 148). Although functional VDCCs have been identified in cultured and freshly isolated astrocytes from neonates (132), Carmignoto et al. (22) did not observe VDCC currents in astrocytes in situ. Moreover, the dramatic reduction in activity-induced astrocyte Ca$^{2+}$ signals after ER Ca$^{2+}$ store depletion with cyclopiazonic acid argues against a significant contribution of astrocytic VDCCs. Ca$^{2+}$ entry into astrocytic endfoot does seem to be involved in NVC, as recent evidence from our laboratory indicates that Ca$^{2+}$ entry through transient receptor potential vanilloid 4 (TRPV4) channels contributes to the astrocytic endfoot Ca$^{2+}$ increase to neuronal activation (41).

Neuronal depolarization by EFS in brain slices or somatosensory stimulation in vivo typically generates a single, relatively sustained elevation in astrocyte [Ca$^{2+}$]$_i$, that gradually decays (55, 158, 177). In contrast, Pasti et al. (133) reported that pharmacological stimulation of mGluRs with 1-aminocyclopentane-1,3-dicarboxylic acid (t-ACPD) induced oscillatory Ca$^{2+}$ signals in astrocytes in brain slices; however, higher concentrations of t-ACPD elicited a single rise in astrocyte [Ca$^{2+}$]$_i$ with characteristics similar to those seen with EFS in slices and in vivo. Notably, in vivo two-photon imaging demonstrated that the rise in astrocyte [Ca$^{2+}$]$_i$ during somatosensory activation decays and returns to baseline before termination of the stimulus (177). The implications of this observation are not clear, but it could be indicative of Ca$^{2+}$-dependent inhibition of IP$_3$Rs or some form of negative feedback from astrocytes to neurons. The astrocytic Ca$^{2+}$ response to neural activation is strongly correlated with neuronal activity and is dependent on stimulus frequency. In the somatosensory cortex in vivo, both neuronal activity (measured by local field potential recording) and astrocyte [Ca$^{2+}$]$_i$ exhibit a bimodal dependence on stimulus frequency, increasing to a peak response and then declining with further increases in stimulus frequency (177).

A rise in endfoot [Ca$^{2+}$]$_i$ is critical for astrocyte-dependent vasodilation (159). Yet, the relative contribution of astrocyte-mediated, Ca$^{2+}$-dependent signaling to the overall hyperemic response to neural activation is an area of ongoing controversy. Using a mouse knockout model of the IP$_3$R believed to be the primary subtype in astrocytes (IP$_3$R2), two very recent reports by Nizari et al. (126) and Takata et al. (164) suggested that astrocytic IP$_3$Rs and Ca$^{2+}$ signaling are not required for full elaboration of neuronal activity-induced vasodilation in the mouse cortex. However, another recent report (72) using the same knockout model provided compelling evidence showing that evoked vasodilation is lost. It is noteworthy that in all of these studies, Ca$^{2+}$ signaling was examined in the astrocyte soma and not in the astrocytic processes. Data derived largely from knockout mouse strains should be considered cautiously due to possible compensation during development. Indeed, it is difficult to imagine that any major cell type, including astrocytes, could function without IP$_3$R-dependent Ca$^{2+}$ signaling. Although IP$_3$R2 is the major isoform in astrocytes, other isoforms have been reported (e.g., IP$_3$R1) (83). Moreover, in the case of Nizari et al., the results were based largely on the use of a Ca$^{2+}$ indicator with a $K_d$ of 3 μM, which is roughly an order of magnitude greater than previously published estimates of activity-induced increases in astrocytic [Ca$^{2+}$]$_i$. In any case, endfoot-restricted increases in [Ca$^{2+}$]$_i$ produced by photolysis of caged Ca$^{2+}$ evoke arteriolar dilation and increase CBF (62, 163), and there is substantial experimental evidence showing that neuronal activity initiates an increase in astrocytic [Ca$^{2+}$]$_i$. That, upon reaching the endfoot, activates Ca$^{2+}$-dependent pathways to release vasoactive substances that elicit vasodilation. The exact complement of vasoactive substances released from astrocytes to modulate vascular tone and local CBF has not been fully clarified; however, some key mediators have emerged.

One of the first proposed (and still widely touted) astrocyte-derived vasoactive mediators of NVC is PGE$_2$. Early evidence for a role for PGE$_2$ in NVC was provided by a report (49) showing that PGE$_2$ dilates cerebral arteries in vivo. Consistent with this supposition, a subsequent study (188) reported that glutamate stimulates Ca$^{2+}$-dependent PGE$_2$ release in cultured astrocytes. Nonselective inhibition of cyclooxygenase (COX)-1 and COX-2 by indomethacin attenuates the increase in CBF to electrical hindpaw and whisker stimulation (7, 93); selective inhibition of COX-1 with SC-560 prevents the increase in CBF to endfoot Ca$^{2+}$ uncaging (163); and both SC-560 and the COX-2 inhibitor NS-398 attenuate the CBF response to whisker stimulation (93, 98, 125, 187). However, recent evidence suggests that COX metabolism in neurons, not astrocytes, is responsible for prostanoid-mediated effects during NVC in the somatosensory cortex (93). Moreover, single cell RT-PCR experiments found mRNA for COX-1 in only 10% of astrocytes examined in the rat whisker barrel cortex and did not detect COX-2 at all (93). In contrast, COX-2 is expressed constitutively in populations of pyramidal neurons within the cortex that are engaged during NVC (14, 93, 185). Importantly, Dabertrand et al. (32) recently demonstrated that isolated cortical parenchymal arterioles with myogenic tone do not dilate, but instead constrict, to PGE$_2$. Reports (54, 109) of increased CBF to PGE$_2$ in vivo as well as observed effects of COX inhibition on NVC may reflect an effect of PGE$_2$ on neurons or astrocytes, both of which express PGE$_2$ (EP) receptors. Indeed, PGE$_2$ has been shown to stimulate intracellular Ca$^{2+}$ release in cultured hippocampal astrocytes (147). It should also be noted that studies identifying a COX-dependent effect on NVC were modeled using somatosensory stimuli, in which the stimulus is communicated to the somatosensory cortex by ascending glutamatergic afferents. However, in the case of basal forebrain stimulation, which involves cortical activation by incoming cholinergic afferents, or light stimulation in the retina, which involves purinergic afferents, COX inhibition has no effect on NVC (92, 113). These observations support the concept that neuronal COX contributes to NVC and does so in a network-specific manner. An alternate explanation is that PGI$_2$, rather than PGE$_2$, released from neurons or possibly the endothelium may be responsible for COX-dependent effects on NVC, as PGI$_2$ robustly dilates parenchymal arterioles (32). These results convincingly demonstrate that,
while neurally released PGE2 may be involved in NVC at some level, PGE2 is not an astrocyte-derived mediator of parenchymal arteriolar dilation during NVC.

Other mediators likely to be released by astrocytes during NVC are epoxygenesatrienoic acids (EETs; Fig. 1). EETs are generated by cytochrome P-450 epoxygenase metabolism of arachidonic acid. The rise in endfoot [Ca2+]i to neuronal activity stimulates the Ca2+-dependent form of phospholipase A2 (PLA2) to hydrolyze membrane phospholipids and release arachidonic acid. Cultured astrocytes express cytochrome P-450 2C11 epoxygenase and have been shown to produce arachidonic acid and EETs in response to glutamate (2, 154). Parenchymal arterioles reportedly do not dilate to mGluR stimulation in cortical brain slices treated with the PLA2 inhibitor arachidonyl trifluoromethyl ketone (69). Similarly, parenchymal arterioles in brain slices from mice lacking the gene for cytosolic PLA2-α are insensitive to mGluR stimulation (72). However, PLA2 inhibition may have a direct effect on parenchymal arterioles; methyl arachidonyl fluorophosphonate has been shown to dilate arterioles in brain slices, thereby decreasing vasodilatory capacity (41).

With the lack of a conditional and tissue-specific knockout model, it is difficult to determine the precise role of astrocytic endfoot PLA2 in NVC. Selective inhibition of EET formation attenuates parenchymal arteriolar dilation to mGluR stimulation and suppresses the increase in CBF elicited by glutamate, the mGluR agonist (S)-3,5-dihydroxyphenylglycine, whisker stimulation, and electrical stimulation of basal forebrain afferents (2, 13, 92, 99, 151). Pial arterioles have been reported to dilate to 5,6-EET, 8,9-EET, and 11,12-EET regioisomers through activation of large-conductance Ca2+-sensitive K* (BKCa) channels in arterial smooth muscle cells (SMCs) (60).

The Glia Limitans in NVC

NVC does not occur solely at the level of parenchymal arterioles. To sustain elevations in local CBF during neuronal activation, upstream arterial segments must also dilate. The glia limitans is a specialized population of astrocytes that line the pial surface of the brain and signal to pial arteries and arterioles to promote dilation of these larger-caliber vessels upstream of parenchymal arterioles during NVC. Much as astrocytic endfeet are positioned between neurons and parenchymal arterioles, the glia limitans is positioned between cortical neurons and pial arterioles, allowing the glia limitans to communicate signals arising from neuronal populations to the pial circulation.

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Neurovascular signaling through the glia limitans to the pial vasculature appears to involve mechanisms that are both similar to and distinct from those that couple astrocytes to parenchymal arterioles. Neuronal activation produces a rapid dilation of local pial arterioles that can be prevented by selective disruption of the glia limitans by the gliotoxin l-α-aminoadipic acid (t-AAA) (124, 183, 184). As is the case for astrocytes surrounding parenchymal arterioles, astrocytes of the glia limitans have been reported to dilate pial arterioles through astrocytic BKCa channels and smooth muscle Kir channels acting in series. Pial arteriolar dilation in response to in vivo sciatic nerve stimulation (SNS) is nonadditively reduced by ~60% after local inhibition of BKCa channels with paxilline and Kir channels with Ba2+ (130). The mechanism of engagement of BKCa channels is presumably through an elevation in [Ca2+]i, but Ca2+ imaging studies in glia limitans during NVC in vivo or in brain slices are notably lacking.
Inhibition of adenosine receptors has been reported to attenuate the increase in cortical CBF to whisker stimulation by 39% (38) and blunt the increase in cerebellar blood flow to parallel fiber stimulation by 45% (96). Whereas dilation of parenchymal arterioles to astrocytic Ca\(^{2+}\) uncaging in vivo is not sensitive to inhibition of adenosine A\(_1\) and A\(_2\) receptors (163), pial arteriolar dilation to SNS is reduced by about half by inhibition of A\(_2\) receptors (130), suggesting that adenosine-mediated hyperemia during NVC occurs at the level of pial arterioles. This attenuation of pial arteriolar dilation to SNS via adenosine A\(_2\) receptors is not further augmented with BK\(_{Ca}\) or Kir channel inhibition, suggesting an interaction or convergence between adenosine signaling and the BK\(_{Ca}\)-Kir pathway in this response. It has been suggested that this interaction may occur through adenosine A\(_2\) receptor-mediated K\(^+\) channel phosphorylation via PKA (130), but this has not been confirmed. Adenosine strongly dilates pial arteries through direct activation of A\(_2\) receptors on SMCs (44, 87). Adenosine A\(_2\) receptor-dependent pial arteriolar dilation during NVC appears to be primarily mediated by AMP and adenosine generated by the enzymatic conversion of released ATP (174). Although active neurons release ATP, the source of ATP that contributes to pial arteriole dilation during NVC is likely glia limi\(\text{t}\)ants astrocytes, since dilution of pial arterioles to SNS is almost entirely prevented by 1-AAA, and astrocytes readily release ATP in response to an increase in [Ca\(^{2+}\)]\(_i\) (17, 66, 183).

There is also evidence showing that the glia limi\(\text{t}\)ants mediates neurovascular signaling to pial arterioles through the release of carbon monoxide (CO). CO, which is generated endogenously by heme oxygenase-mediated metabolism of heme, dilates pial arterioles through activation of BK\(_{Ca}\) channels on SMCs (76). Glutamate and ADP applied to the cortical brain surface have been demonstrated to increase heme oxygenase-2-dependent CO production and dilate pial arterioles in newborn pigs in brain slices and in vivo, effects that are eliminated by disruption of the glia limi\(\text{t}\)ants with 1-AAA (79, 94, 95). The majority of studies identifying CO as a glia limi\(\text{t}\)ants-derived neurovascular signaling molecule have been performed in neonates, so it is unclear what role CO plays in neurovascular signaling in the adult brain.

**Neurons in NVC**

After engagement by afferent pathways, cortical excitatory neurons and interneurons release substances that can directly or indirectly influence vascular tone to modulate CBF. It is evident that the mediators released vary according to the neuronal network activated and the frequency of the stimulus (Fig. 1) (50). In other words, signaling mechanisms mediating NVC are neuronal network dependent as well as being stimulus frequency dependent.

**Signaling from afferent and cortical excitatory neurons in NVC.** Ascending afferent neurons arising from subcortical areas of the brain that terminate in the cerebral cortex activate cortical neurons via the release of network-specific neurotransmitters that have intrinsic vasoactive properties. These neurotransmitters include, among others, ACh and serotonin (5-HT), which have the potential to dilate and constrict parenchymal arterioles directly, respectively (33, 175). The basal forebrain is the major source of cholinergic input to the cortex, and some basal forebrain afferents have been shown to project directly to intracerebral microvessels, including parenchymal arterioles, capillaries, and possibly veins (171). The cortical hyperemic response to basal forebrain stimulation has been shown to partially depend on local ACh release and non-neuronal NO, leading to the suggestion that ACh released from these afferents during NVC directly stimulates vasodilatation through activation of eNOS (see Fig. 1A, top) (186). However, a role for direct neurovascular signaling from ascending subcortical afferents during NVC is unclear, as it is now understood that ACh- and NO-dependent effects may occur at the level of pyramidal neurons and interneurons (92). Subcortical afferent activity is critical for the elaboration of NVC insofar as it activates cortical neurons, but the CBF response to somatosensory stimulation has been attributed to neural processing within the cortex rather than to direct signaling from incoming subcortical afferents (57).

Activation of cortical pyramidal neurons by afferent signals results in the synaptic release of the excitatory neurotransmitter glutamate (Fig. 1). The astrocyte-mediated portion of the hyperemic response to neuronal activity has, to this point, been largely attributed to glutamate binding to astrocytic G\(_{\text{q}}\)-coupled mGluRs. Notwithstanding the recent study by Sun et al. (160) calling this paradigm into question, there is abundant evidence in support of a role for astrocytic mGluRs in NVC. Astrocytes also express N-methyl-d-aspartate (NMDA) and \(\alpha\)-amino-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionotropic glutamate receptors (iGluRs), and the interaction of glutamate with these receptors produces astrocytic Ca\(^{2+}\) signals (100, 101, 150). However, cortical application of NMDA or AMPA receptor inhibitors does not suppress the astrocytic Ca\(^{2+}\) response to whisker stimulation in vivo (177). In contrast, in the brain stem nucleus tractus solitarius, AMPA blockade prevents the rise in [Ca\(^{2+}\)]\(_i\) in astrocytes in response to electrical stimulation of vagal nerve afferents (110). NMDA and AMPA receptor antagonists have also been shown to reduce the cortical hyperemic response to basal forebrain stimulation by ~30% (Fig. 1A); this effect was not further augmented by EET inhibition, suggesting it occurs upstream of astrocytes (92). These findings indicate that the involvement of astrocytic iGluRs in NVC responses is network dependent.

Whereas NMDA/AMPA receptor inhibition does not block the astrocytic Ca\(^{2+}\) response to whisker stimulation, NMDA receptor inhibition has been reported to decrease the associated CBF response (93). It has been hypothesized that this effect occurs by preventing the activation of cortical pyramidal neurons by glutamate (Fig. 1B), suggesting that for this neuronal network, the effect of NMDA receptor antagonism on CBF response reflects diminished excitatory neuronal activation. If true, however, suppressed activation of pyramidal neurons would be expected to attenuate downstream astrocytic Ca\(^{2+}\) responses as well. A possible explanation for this discrepancy, namely, an effect of NMDA receptor blockade on whisker stimulation-induced CBF increases in the absence of an effect on astrocytic Ca\(^{2+}\), may be that synthetically released glutamate activates NMDA receptors on NOX-expressing interneurons, stimulating the release of NO, which dilates parenchymal arterioles (Fig. 1B, bottom). The role of interneurons in NVC will be discussed in detail below.

Another neurotransmitter released by activated excitatory neurons is ATP (91, 131, 180). ATP stimulates astrocytic Ca\(^{2+}\)
signals through the activation of G protein-coupled metabo-
tropic P<sub>2</sub>Y purinergic receptors, stimulating the PLC-β-depend-
dent formation of IP<sub>3</sub> and release of Ca<sup>2+</sup> into the cytosol through IP<sub>3</sub>Rs (Fig. 1) (25, 51, 58). ATP-induced increases in astrocytic [Ca<sup>2+</sup>]<sub>i</sub> have been linked to NVC in the olfactory bulb and retina, although it should be noted that in the olfactory bulb, this mechanism was associated with vasoconstriction, making its physiological relevance questionable (123, 167).

A recent study has demonstrated that adenosine, a powerful dilator of cerebral arterioles (78), is released from electrically activated postsynaptic CA1 neurons (102). While postsynaptic adenosine release in this study was functionally correlated with synaptic depression, it could potentially also contribute to the vasodilatory response to neuronal activity.

**Signalining from interneurons in NVC.** Interneurons also play a significant role in neurovascular signaling. Interneurons are believed to act as integrators of neuronal activity and have been demonstrated to make direct contact with cortical microvessels and astrocytic processes (24, 26, 173). Depending on the type and frequency of the stimulus, incoming affenter signals in the cortex engage specific populations of GABA interneurons, which release vasoactive substances capable of directly dilating or constricting arterioles as well as neurotransmitters that indirectly affect vascular tone through the modulation of excitory neurons or astrocytes. These populations include interneurons containing VIP, parvalbumin, somatostatin (SOM) and/or NPY, choline acyltransferase (which synthesizes ACh), and NOS/NPY. Cauli et al. (24) found that direct electrical stimulation of individual VIP or NOS/NPY interneurons dilated parenchymal arterioles in brain slices, whereas direct stimulation of SOM interneurons produced vasoconstriction. Perfusion with VIP or the NO donor diethylamine-NONOate potently dilated preconstricted parenchymal arterioles in brain slices, supporting the potential for a direct action of these substances on vascular tone; however, arterioles in brain slices did not constrict when perfused with SOM. Of interest, constrictions observed with electrical stimulation of SOM interneurons were highly localized to points of contact between arterioles and interneurons, creating a vascular sphincter-like effect. This observation supports a model in which localized constriction accompanies dilation during NVC, redirecting blood flow to more specifically target activated networks (Fig. 1B, top). SOM and VIP have also been found to increase [Ca<sup>2+</sup>]<sub>i</sub> in astrocytic endfeet, indicating that the release of these substances from interneurons may contribute to NVC indirectly through an effect on astrocytes (158).

Basal forebrain stimulation initiates cholinergic-dependent activation of not only COX-2 pyramidal neurons but also SOM and NOS/NPY GABA interneurons (Fig. 1A) (24). It is thought that activation of these interneurons contributes to NVC through released GABA, which binds to GABA-A receptors in downstream GABAergic inhibitory interneurons, relieving GABA-mediated inhibition of pyramidal neuron activity and thereby increasing excitatory neuronal activity and, consequently, local CBF (88). Whisker stimulation, which is communicated to the cortex via glutamatergic thalamocortical afffers, engages VIP/choline acyltransferase interneurons (Fig. 1B). As with basal forebrain stimulation, the role of these interneurons in the hyperemeric response to whisker stimulation is attributed to GABA-A receptor-mediated alleviation of suppression of pyramidal neuron activity by parvalbumin and calbindin inhibitory interneurons rather than through a direct effect of VIP or ACh on vascular tone (93). Moreover, GABA released from GABAergic interneurons can induce Ca<sup>2+</sup> signaling in astrocytes through stimulation of astrocytic GABA-A receptors. GABA-A receptor inhibition reportedly attenuates the CBF increase to basal forebrain stimulation upstream of EET formation, suggesting an astrocyte-mediated effect (92). GABA can also directly dilate parenchymal arterioles (albeit to a limited extent) in brain slices, suggesting multiple contributions to NVC of GABA signaling from interneurons (52, 111). The cortex also receives serotonergic affenter input from brain stem nuclei, and stimulation of cortical interneurons expressing 5-HT<sub>3</sub>A receptors with the agonist 1-(3-chlorophenyl)biguanide hydrochloride induces NO-mediated dilation and NPY-mediated constriction of parenchymal arterioles (135).

It has long been appreciated that NO contributes to both resting CBF and NVC. Inhibition of NOS has been shown to reduce the increase in CBF in the cortex induced by stimulation of the sciatic nerves (127), basal forebrain (127), hindpaw (86), or facial whiskers (37) and in the cerebellum by stimulation of parallel fibers (74); in each case, the reduction was ~50%. Moreover, tissue NO has been shown to rapidly increase in the somatosensory cortex of rats in response to electrical forepaw stimulation and is temporally correlated with an increase in CBF (16). It is thought that neurons are largely the source of NO in NVC, insofar as CBF responses to neuronal activation are blunted in the presence of the neuronal NOS inhibitor 7-nitroindazole (28, 153) and in mice lacking neuronal NOS but not in eNOS-deficient mice (4, 86, 103). More specifically, studies (112, 141, 146, 170, 172) have suggested that NO is released during neuronal activation by NO-expressing GABA interneurons in response to stimulation of muscarinic ACh receptors (mAChRs) by ACh released from cholinergic affecters (Fig. 1A), stimulation of NMDA receptors by glutamate released from glutamatergic affecters (Fig. 1B), or stimulation of α-/β-adrenoreceptors by NE released from adrenergic affecters. Additionally, NOS expression has been reported in CA1 pyramidal neurons in the hippocampus, so it is possible that NO may be produced and released by excitatory neurons as well (179). NO production by eNOS in vascular endothelial cells in response to mAChR stimulation by neurally released ACh may also contribute to the CBF response to neuronal activation (47). Moreover, the effect of NOS inhibition on NVC may be partly due to an effect on the baseline diameter of parenchymal arterioles. NOS inhibition significantly reduces resting CBF in mice and rats (70, 138) and has been shown to constrict parenchymal arterioles in rats by 14–36% (29, 84, 165). This vasoconstriction, or increase in vascular tone, could alter the responsiveness of parenchymal arterioles to subse-
quent incoming signals during NVC. Indeed, evidence has been presented showing that the magnitude of stimulus-evoked dilation of parenchymal arterioles in brain slices depends on their resting tone (13), indicating that an effect of NOS inhibition on resting arteriolar tone may contribute to altered NVC responses.

**Pericytes in NVC.** Pericytes are contractile cells that are adjacent to, and embedded in the basal lamina of, capillaries. Pericyte projections wrap around capillaries and are capable of regulating
capillary diameter by contracting or relaxing. Cultured pericytes contract to 5-HT (82) and NE (106) and relax to NO (65), adenosine (107), VIP (106), and PGI2 (39), all of which can be released by activated neuronal networks [for a review, see Hamilton et al. (68)]. In cerebellar slices, NE stimulates pericyte-mediated constriction of capillaries, and subsequent application of glutamate relaxes pericytes to cause capillary dilation (134). Moreover, GABA receptor inhibition contracts pericytes and reduces capillary diameter in the whole retina, suggesting a relaxing effect of GABA signaling on pericyte tone. The contractile ability of pericytes has been confirmed in vivo and shown to produce alterations in red blood cell flow in capillaries (53). However, Fernandez-Klett et al. (53) found that cortical capillary diameter in vivo did not change in response to an increase in neuronal activity induced by the GABA-A receptor antagonist bicuculline; also, while an increase in capillary diameter was observed during cortical spreading depolarization, it was found to occur passively as a result of upstream arteriolar dilation. These findings indicate that, while neurovascular signaling through pericytes to capillaries may occur under certain circumstances, it does not contribute significantly to NVC. Nevertheless, pericytes play a critical role in maintaining the blood-brain barrier, which is vital for maintaining the milieu required for neurovascular regulatory mechanisms to function properly.

**Neurovascular Dysfunction in Hypertension**

Some reports (46, 85, 117, 121) have indicated that resting CBF is reduced in hypertension and progressively declines over time, whereas others (30, 71, 145) have found that resting global and regional CBF in hypertension is unchanged from that in normotensive controls. The observation of unchanged resting CBF in hypertension is likely attributable to myogenic autoregulation, which resets to higher pressure levels in hypertension but remains functional over a similar magnitude of pressure change (10, 156, 157). Impaired NVC (impaired ability to increase local CBF in response to elevated neuronal activity) has been observed in hypertension and may be the critical consideration in linking hypertension to cognitive dysfunction. Still, the impact of hypertension on neurovascular signaling and regulation in the brain has not been extensively investigated, and mechanistic insights have only begun to emerge in the last decade. It is unclear whether hypertension itself impairs neurovascular regulation or if ANG II signaling is the real culprit behind the apparent hypertensive neurovascular dysfunction. Available evidence, though limited, suggests the latter may be true. Hypertension induced acutely by intravenous ANG II infusion, or chronically by subcutaneous ANG II infusion via osmotic pumps, blunted the rise in cortical CBF to whisker stimulation in mice by 65% (81). However, direct cortical application of ANG II produced the same attenuation in NVC without increasing arterial pressure. Similarly, chronic, subpressor infusion of ANG II disrupts NVC before the development of hypertension (20). Moreover, chronic infusion of phenylephrine raises arterial pressure to the same extent as ANG II infusion but has no effect on the CBF response to whisker stimulation, suggesting it is not hypertension but ANG II that disrupts NVC (81). Impaired NVC in retinal arterioles has also been demonstrated in monkeys subjected to an ANG II-dependent, two-kidney/two-clip model of hypertension (59). ANG II is centrally involved in the pathogenesis of many forms of human hypertension, as evidenced by the prevalence and efficacy of antihypertensive therapies that target the renin-angiotensin-aldosterone system (34). Therefore, even if impaired NVC is specific to ANG II signaling, it is highly relevant to human hypertension.

NVC has not been well studied in genetic hypertension. Clozel et al. (30) found that the increase in CBF (measured by radioactive microspheres) to bicuculline-induced seizure activity was blunted in spontaneously hypertensive rats (SHRs) compared with normotensive control rats and that the blunted hyperemic response in SHRs was normalized by treatment with the angiotensin-converting enzyme inhibitor cilazapril. This observation suggests that even in genetic hypertension, ANG II signaling contributes to neurovascular dysfunction; however, a bicuculline-induced seizure is not a physiological condition. A very recent study by Calcagno et al. (18) examined physiological NVC in the SHR model. Using laser speckle imaging, they found that the peak and duration of the somatosensory cortical CBF response to whisker stimulation were attenuated in SHRs at 20 and 40 wk of age compared with normotensive control rats. Impairment of NVC in 40-wk-old SHRs was not reversed by 10-wk treatment with an antihypertensive drug [verapamil (VDCC antagonist) or losartan (ANG II receptor antagonist)] to normalize blood pressure, suggesting that other factors may be involved in altered NVC at this stage of hypertension (17). Much additional work is required to characterize neurovascular function in genetic and other models of hypertension to obtain a clearer understanding of NVC phenotypes and the underlying mechanisms central to NVC dysfunction in these models.

The disruption of NVC by ANG II is dependent on ANG II type 1 receptor (AT1R) signaling and downstream ROS production by NADPH oxidase (Nox), an enzyme that generates O2− (80). AT1Rs and gp91phox, a subunit of Nox, were found to localize to endothelial cells and adventitia, but not SMCs, of mouse parenchymal arterioles, suggesting that impairment of NVC by ANG II is due to O2− formation in the vascular endothelium (80). Capone et al. (19) reported that ANG II-stimulated ROS formation by Nox is dependent on a permissive role of constitutive COX-1-derived PGE2 from microglia acting on prostaglandin EP1 receptors in vascular endothelial cells; however, the mechanism of interaction between these pathways is unknown. In chronic, slow pressor ANG II-dependent hypertension, cerebral microvascular oxidative stress is also induced by increased vascular endothelin-1 production as a result of ANG II-stimulated arginine vasopressin release from the hypothalamic paraventricular nucleus (21).

The mechanisms by which vascular oxidative stress interrupts neurovascular signaling in the brain are not known. The simplest explanation would be that this effect relates to a loss of NO bioavailability and impaired vasodilation resulting from increased scavenging of NO through a reaction with O2−, because, as discussed above, NO clearly plays a significant role in NVC. However, the source of NO produced during NVC (in the somatosensory cortex, at least) is believed to be neurons, specifically NOS interneurons, as opposed to the vascular endothelium (4). The NO donor S-nitroso-N-acetyl penicillamine induces an increase in CBF in ANG II hypertensive mice, indicating that hypertensive cerebral arterioles retain their NO responsiveness and should still be able to dilate to neurally
released NO (81). While an eNOS-dependent dilation mediated by ACh released from active cholinergic neurons has been proposed, and this could account for impaired vasodilation during NVC (186), a direct vascular action of ACh during NVC has not been experimentally validated and does not likely make a large contribution to the overall response, particularly in noncholinergic afferent neuronal networks. Therefore, a loss of endothelium-derived NO per se is unlikely to play a large role in ANG II-dependent impairment of NVC.

It is likely that the effect of ANG II hypertension on NVC is not so much due to a loss of endothelial NO bioavailability as it is to the formation of other highly reactive species. In addition to vascular oxidative stress, ANG II-dependent hypertension produces cerebral vascular nitrosative stress, dramatically increasing the levels of 3-nitrotyrosine, a marker for ONOO$^-$ (63). Cerebral vascular ONOO$^-$ formed in response to ANG II was found to be produced by the reaction of eNOS-derived NO with Nox2-derived O$_2^-$ (63). Pretreatment of the somatosensory cortex with a scavenger or decomposition catalyst of ONOO$^-$ prevents the effect of ANG II on the hyperemic response to whisker stimulation (63). This observation suggests that the ANG II-mediated attenuation in NVC is entirely dependent on ONOO$^-$. The pathways targeted by ONOO$^-$ that produce neurovascular dysfunction are unknown, although ONOO$^-$ has been demonstrated to disrupt vasodilatory responses in pial arteries to decreased intraluminal pressure, calcitonin gene-related peptide, and an ATP-sensitive K$^+$/H$^+$ channel opener (35). Notably, in this latter study, ONOO$^-$ did not alter pial artery dilation to K$^+$. ONOO$^-$ was also found to constrict pial arteries at low concentrations but dilate at concentrations of $>1$ μM (105). Furthermore, ONOO$^-$ mediates the cerebral vascular dysfunction associated with aging through activation of poly(ADP-ribose) polymerase (36). ONOO$^-$ is a highly reactive and potentially destructive molecule that can compromise the function of cellular proteins through nitrosylation (97). A critical area for future research will be elucidating the cellular targets of ONOO$^-$ in the cerebral vasculature in ANG II hypertension.

Therefore, it should be noted that, although the loss of endothelial NO as a vasodilator may not be responsible for disrupted NVC in hypertension, endothelial NO provides a substrate for the formation of damaging radicals that may compromise the structural and functional integrity of the cerebral circulation. Moreover, endothelial NO makes a significant contribution to resting cerebral vascular tone and CBF, and reduced endothelial NO bioavailability in the cerebral vasculature could promote chronic hypoperfusion of the brain in hypertension (84, 104).

Hypertension and Cerebral Vascular Structure and Reactivity

Although the attenuation of NVC by ANG II can be observed acutely and in the absence of hypertension, chronic hypertension compromises cerebral vascular structural integrity and reactivity as well [for a recent review, see Pires et al. (137)]. Chronic hypertension induces vascular hypertrophy with increases in extracellular matrix deposition and inward remodeling as well as an associated decrease in lumen diameter in pial and parenchymal arteries and arterioles (3, 11, 27, 40, 119, 168). Pial arteries, measured in vivo through a closed cranial window, are more constricted at rest and after hypercapnic challenge in SHRs than in normotensive rats (77). It stands to reason that the maximum pial artery diameter elicited by neuronal stimulation may also be diminished in hypertension, but this has not been studied. Impaired NVC at the level of pial arteries/arterioles in hypertension could have a significant impact on cerebral homeostasis, as upstream dilation is necessary to sustain adequate parenchymal perfusion. Hypertension also increases blood-brain barrier permeability, primarily at the level of parenchymal arterioles (118–120, 129, 143). These changes produce arterial necrosis and cerebral edema, which clearly have disastrous consequences on vascular reactivity and neurovascular signaling in the brain, although empirical evidence to this effect is limited (27, 118, 128, 152). In addition to endothelial dysfunction (which is a universal hallmark of hypertensive cerebral arteries), impaired vascular reactivity of pial arteries to 5-HT and high K$^+$ concentration has been demonstrated in SHRs (181), and isolated pial artery SMCs from hypertensive animals were found to be more sensitive to the VDCC agonist Bay K 8644 (15, 178). Furthermore, ATP-mediated dilation of carotid arteries (73) and K$^+$-mediated dilation of pial arteries (108) are reportedly diminished in SHRs, suggesting that these dilatory pathways may also be impaired in vascular segments (pial and parenchymal arterioles) involved in CBF responses to neural activity.

Hypertension and Astrocytes, Neurons, and Pericytes

Other cell types that make up the neurovascular unit in the brain exhibit pathological changes in hypertension that are, in most cases, secondary to the loss of structural integrity of the cerebral vasculature. The progression of hypertension in genetically hypertensive SHRs and stroke-prone SHRs is associated with pericyte degeneration, which correlates with increased blood-brain barrier permeability and astrocyte hypertrophy and fibrosis (3, 144, 161). Tagami et al. (161) found that fibrotic astrocytes in stroke-prone SHRs were localized adjacent to open interendothelial junctions, suggesting that the loss of blood-brain barrier integrity promotes astrocyte fibrosis (161). Furthermore, neuron number is decreased in SHRs, and dead neurons are observed adjacent to fibrotic astrocytes (144, 162). Exposure of cultured astrocytes to endothelial cell-conditioned medium from stroke-prone SHRs stimulates greater astrocyte proliferation than that from normotensive rats, indicating that endothelial cells release mitogenic, proliferative signals in response to high intravascular pressure. In ANG II-dependent hypertension, ANG II may have direct effects on neurons and astrocytes. In medullary and cerebellar, but not cortical or hypothalamic, astrocytes from neonatal mice, ANG II stimulates a PLC/IP$_3$-mediated increase in Ca$^{2+}$ concentration via AT$_1$R as well as PGI$_2$ release (166). These findings suggest that ANG II can have region-specific effects on astrocyte function; however, cautious interpretation is warranted, as responses in neonates are not typically accurate representations of adult responses. Furthermore, chronic ANG II infusion has been found to increase O$_2^-$ formation in neurons in addition to the cerebral vasculature, suggesting that the inhibitory effect of ANG II on NVC may also reflect effects on neurons.
Summary

Neurovascular regulation of CBF is a highly dynamic, complex, coordinated process involving the modulation of cerebral vascular tone by signaling within and between neuronal subpopulations (extrinsic perivascular nerves, excitatory neurons, and interneurons), astrocytes, and pericytes. Neurovascular signaling matches substrate delivery by the blood to metabolic demand, maintains the proper milieu for neural processing, and protects brain cells from damage by physical forces and neurohumoral factors within the vasculature. The destructive effects of hypertension on the brain illustrate the critical importance of neurovascular signaling to brain function. Hypertension initiates a chain of events that starts with structural and functional breakdown of the cerebral vasculature and leads to disruption of neurovascular unit microanatomy, loss of neurovascular regulation, and, ultimately, neurodegeneration. As insights are made into the physiological mechanisms of neurovascular regulation, significant gaps remain to be filled in our understanding of the mechanisms linking hypertension to neurovascular dysfunction in the brain. A major imperative moving forward is to elucidate the mechanisms by which vascular oxidative stress impairs neurovascular signaling and to better understand the role of the endothelium in neurovascular signaling. It is also necessary to further characterize NVC responses in genetic and other non-ANG II-dependent hypertensive models and to investigate NVC in human hypertensive subjects using blood oxygen level-dependent functional MRI and other dynamic imaging modalities. Impaired blood oxygen level-dependent hemodynamic signals elicited in response to neural activation in poststroke human subjects (90) or human level-dependent hemodynamic signals elicited in response to neural activation in poststroke human subjects (90) or human subjects with extracerebral and intracerebral artery disease (stenosis) (69) have been reported, but these investigations have not been made in hypertensive patients. A more thorough understanding of neurovascular dysfunction in hypertension will further illuminate the role of ANG II signaling versus other mechanisms and identify optimal therapeutic strategies for preventing or reversing hypertensive neuropathy. Insights into neurovascular dysfunction in hypertension may also shed light on pathogenic mechanisms of other forms of small vessel disease of the brain, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Evidence of increased age-related white matter lesions in hypertensive patients expressing common variants of Notch3, the gene associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (149), suggests that hypertension may provide a permissive background for the manifestation of genetic small vessel disease-associated neuropathy, or vice versa.

It is increasingly clear that preservation of the brain requires preservation of vascular function and regulation, not only in hypertension but also in other progressive neurodegenerative diseases, such as Alzheimer’s disease and dementia, as well as acute neurologic pathologies like subarachnoid hemorrhage and stroke (8, 23, 64, 89, 90). A thorough understanding of cerebral vascular physiology and neurovascular signaling in the brain is essential to identifying therapeutic neuroprotection strategies.

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