Review Article

The role of neuroeffector mechanisms in cerebral hyperperfusion syndromes

ROBERT MACFARLANE, M.B., F.R.C.S., MICHAEL A. MOSKOWITZ, M.D.,
DANOS E. SARAS, M.D., EROL TASDEMIRGULU, M.D., ENOCH P. WEI, PH.D., AND
HERMES A. KONTOS, M.D., PH.D.

Neurosurgery and Neurology Services, Massachusetts General Hospital, Harvard Medical School,
Boston, Massachusetts, and Division of Cardiology, Department of Medicine, Medical College of
Virginia, Richmond, Virginia

Cerebral hyperperfusion, a state in which blood flow exceeds the metabolic needs of brain, may complicate a number of neurological and neurosurgical conditions. It may account for the propensity with which hemorrhage, cerebral edema, or seizures follow embolic stroke, carotid endarterectomy, or the excision of large arteriovenous malformations, and for some of the morbidity that accompanies acute severe head injury, prolonged seizures, and acute severe hypertension. Hyperperfusion syndromes have in common acute increases in blood pressure, vasodilatation, breakdown of the blood-brain barrier, and the development of cerebral edema. These common features suggest the possibility that they share the same pathogenic mechanisms. It was believed until recently that reactive hyperemia was caused primarily by the generation of vasoactive metabolites, which induced vasodilatation through relaxation of vascular smooth muscle. However, the authors have recently established that the release of vasoactive neuropeptides from perivascular sensory nerves via axon reflex-like mechanisms has a significant bearing upon a number of hyperperfusion syndromes. In this article, the authors summarize their data and discuss possible therapeutic implications for blockade of these nerves or their constituent neuropeptides.

KEY WORDS • ischemia • hyperperfusion syndrome • trigeminal nerve • calcitonin gene-related peptide • substance P

RESTORATION of cerebral circulation following a period of ischemia results in a transient phase of blood flow in excess of metabolic requirements, which is generally followed by a period of hypoperfusion. A third phase of delayed hyperemia may develop some days later, but is probably a consequence rather than a cause of tissue injury.127

Reactive hyperemia was characterized in 1925 by Lewis and Grant,79 who observed the phenomenon during reperfusion following acute or chronic vascular occlusion of the limbs. It has been reported since in many tissues, including myocardial22 and skeletal muscle, intestine,100 kidney,2 and brain.50,61,120,127 The term “luxury perfusion syndrome” was coined by Lassen14 to describe overabundant cerebral blood flow (CBF) relative to metabolic needs. Hyperperfusion may compound the original insult by exacerbating cerebral edema or by causing intraparenchymal hemorrhage.48,93 It may follow diffuse or local brain injury, and may either be confined to the area of injury or be widespread. In general, hyperemia is more profound in gray than white matter.42

This brief review will consider the major syndromes accompanied by cerebral hyperperfusion and will examine underlying metabolic and neurogenic mechanisms. Attention will focus on the importance of nerve pathways that innervate brain blood vessels from extrinsic sources and, in particular, the trigeminalvascular system. Recently published data suggesting the importance of axon-like reflexes to the development of cortical hyperemia will be emphasized and potential therapeutic strategies discussed.

Cerebral Hyperperfusion Syndromes

Cessation of blood flow is not a prerequisite for the development of hyperemia. Hyperperfusion has been
demonstrated following recovery from systemic hypotension and hypocapnia.\textsuperscript{128,145} Ischemia lasting as brief a duration as 30 seconds is sufficient to elicit a threeto-fourfold increase in CBF.\textsuperscript{42}

**Carotid Endarterectomy**

A hemodynamic rather than embolic etiology for cerebral infarction after carotid endarterectomy was postulated by Fisher, \textit{et al.}\textsuperscript{36} Carotid stenosis in excess of 70\% is sufficient to cause a reduction in CBF\textsuperscript{115,169} and an alteration in cerebral vasoreactivity.\textsuperscript{131} Cerebral hyperperfusion syndrome was one of the most frequent complications in a series of 1145 carotid endarterectomies performed at the Mayo Clinic.\textsuperscript{145} Cerebral blood flow may increase dramatically during surgery, whereas in other cases hyperperfusion does not manifest for several days.\textsuperscript{13,124} Patients at greatest risk are those with either bilateral internal carotid artery stenosis greater than 95\%, unilateral carotid artery occlusion with a contralateral high-grade stenosis, unilateral very high-grade stenosis with poor collateral cross-filling, or chronic cerebral ischemia.\textsuperscript{128,133,139,141-143}

Clinical features of hyperperfusion include severe unilateral headache, face and eye pain, seizures, and cerebral edema.\textsuperscript{13,127,135,152} Of patients with this syndrome, approximately 40\% will develop intracerebral hemorrhage,\textsuperscript{129} a complication with a mortality rate of 36\%.\textsuperscript{124} Histologically, the condition is analogous to hypertensive encephalopathy. Affected brains show proliferation of endothelial and smooth-muscle cells and edema of neuropil.\textsuperscript{13}

**Embolic Stroke**

The majority of hemorrhagic infarcts are of embolic origin,\textsuperscript{35} suggesting that migration of an embolus at some time after impaction leads to reperfusion of an ischemic area with resultant intraparenchymal hemorrhage.\textsuperscript{187} In a clinical study of acute stroke, cortical infarcts were associated consistently with large areas of mild to severe hyperemia.\textsuperscript{188} Focal hyperemia of three distinct types developed in 39\% of a group of 41 patients in whom CBF was measured within 3 days of completed stroke. Border-zone hyperemia occurred in areas surrounding infarcts, while postischemic hyperemia was observed in patients in whom recanalization of an occluded vessel had occurred. In a third group, hyperemia developed at sites remote from the ischemic area. An analogous situation may develop following surgical revascularization procedures for cerebral ischemia, such as superficial temporal to middle cerebral artery anastomosis.\textsuperscript{50,139}

**Surgery for Arteriovenous Malformations**

High blood flow through an arteriovenous malformation (AVM) may cause hyperperfusion of surrounding brain tissue\textsuperscript{6} of sufficient magnitude to manifest as ischemia.\textsuperscript{72,82,96} Abrupt obliteration of the shunt may cause fulminant hyperemia.\textsuperscript{24,106} The term "normal perfusion pressure breakthrough" was coined by Spetzler, \textit{et al.}\textsuperscript{48} to describe the malignant edema and hemorrhage that may develop. Dynamic measurements of CBF have shown increased perfusion following occlusion of even modest AVM's.\textsuperscript{10} Hyperperfusion has been reported also as a complication of surgical treatment of vein of Galen aneurysms.\textsuperscript{99} Supportive evidence for the syndrome as a distinct entity, rather than as a consequence of surgical trauma, comes from two sources. First, hyperperfusion syndrome can be generated experimentally by the obliteration of carotidjugular fistulas.\textsuperscript{97-99,140} Second, patients occasionally develop cerebral hemorrhage at sites remote from the operative field, but which are within the vascular territory supplied by the AVM.\textsuperscript{139}

**Head Injury**

Fluctuating hyperemia is a common sequela of acute severe head injury.\textsuperscript{32} It is thought that the metabolic demands of contused brain are lower than normal because of depressed cell function, and that flows of only 20 ml/100 gm/min are sufficient to sustain brain function.\textsuperscript{32} Reactive hyperemia is associated with a poor prognosis.\textsuperscript{34,87,123,133,134} In a clinical study of 23 patients with severe acute head injury, Enevoldsen, \textit{et al.},\textsuperscript{32} observed that hyperemia increased at times of clinical deterioration and decreased during the recovery period. In patients who became alert, hyperperfusion was replaced by low flow values.

Hyperemia cannot simply be a consequence of impaired CBF autoregulation for two reasons. First, head-injured patients with reduced flow also may have impaired autoregulation.\textsuperscript{190} Second, hyperemia occurs in patients with cortical lacerations or contusions, but not in patients with isolated brain-stem lesions.\textsuperscript{32} In the light of these observations, attempts were made to decrease CBF by pronounced hyperventilation. This proved unsuccessful, probably because CBF decreases in intact regions but increases in damaged areas via an "inverse steal" phenomenon.\textsuperscript{33,122}

**Seizures**

Increases in CBF are detectable within seconds of the onset of generalized seizures.\textsuperscript{37,73,123} Although some hyperperfusion reflects systemic hypertension and the loss of autoregulation, CBF may exceed tissue demands for oxygen by 100\% to 800\%.\textsuperscript{77,94}

**Elevation of Intracranial Pressure**

In 1928, Wolff and Forbes\textsuperscript{57} were the first to report dilatation of pial vessels in response to an increase in intracranial pressure (ICP). Several animal models employ a rapid infusion of fluid into the subarachnoid space as a means of generating cerebral ischemia and postischemic hyperemia.\textsuperscript{42,44,60,81,108-110} Haggendal, \textit{et al.}\textsuperscript{44} have reported that hyperemia develops only when ICP exceeds 50 mm Hg, but that the elevation of CBF subsequently lasts for many hours.
Acute Severe Hypertension

Animals and humans with acute severe hypertension or hypertensive encephalopathy exhibit the characteristic features of the hyperperfusion syndrome. The pathogenesis has been attributed to elevation of blood pressure at a time of loss of autoregulation combined with damage to the integrity of the vessel wall. Cerebral arterioles undergo marked dilatation, which may outlast the duration of the hypertensive episodes by several hours. Vessels develop irregular dilatation and display abnormal reactivity to both arterial hyper- and hypocapnia and to hypotension.

Migraine

Prolonged hyperperfusion has been demonstrated during and after classical migraine attacks, and is thought to represent reactive hyperemia after ischemia. However, no clear temporal relation exists between headache and the development of hyperemia.

Other Precipitating Factors

Other conditions associated with the development of hyperemia include the removal of large mass lesions such as meningiomas, the presence of intracerebral or acute subdural hematomas, bacterial meningitis, and the recovery phase following cardiac arrest.

Metabolic Factors Mediating Hyperperfusion

The generation of vasoactive metabolites during ischemia and the early reperfusion period, such as lactic acid, adenosine, and free oxygen radicals, is known to contribute to hyperperfusion. In addition, because a number of metabolites contribute to opening of the blood-brain barrier, cerebral edema is enhanced. Lactic acid and potassium ions act synergistically to relax cerebrovascular smooth muscle. However, while experimental studies have shown that brain lactate and extracellular potassium return to control values over approximately the same period as the resolution of postocclusive hyperemia, positron emission tomography scans of stroke patients have shown that hyperemia persists for much longer than the correction of acidosis.

During hypoxia, adenosine triphosphate (ATP) is released from brain and causes profound pial arteriolar dilatation. Furthermore, ATP is dephosphorylated in the extracellular space to release adenosine. Adenosine A$_2$ receptors have been found on feline cerebral vessels, and adenosine has been identified as an important link between cerebral metabolism and increases in CBF. The adenosine receptor antagonists theophylline and aminophylline can attenuate cortical hyperemia in experimental models and reduce the vasogenic edema associated with it.

Vascular Sensory Innervation

Pial, dural, and extracranial cephalic blood vessels are surrounded by an adventitial plexus of sensory afferents. The overall pattern is well conserved across species. The circle of Willis, rostral basilar artery, and their major tributaries receive a sensory innervation primarily from the trigeminal nerve. Most cell bodies reside within the ophthalmic division of the ganglion. In primates, fibers pass directly from the trigeminal nerve to the internal carotid artery within the cavernous sinus. The caudal basilar artery and the vertebral arteries and their tributaries are innervated primarily by the upper cervical dorsal root ganglia.

The distribution of sensory nerves is predominantly ipsilateral, with the exception of midline vessels, which receive a significant contralateral innervation. Each ganglion cell projects divergent axon collaterals to innervate multiple large vessels supplying both brain parenchyma and the overlying dura mater. The central projections from perivascular sensory nerves terminate within the trigeminal nuclear complex (mediating pain), the nucleus of the tractus solitarius (a relay for visceral afferent information), the dorsal motor nucleus of the vagus, and the C$_2$ dorsal horn.
The Trigeminovascular System

Trigeminovascular nerves are predominantly unmyelinated C fibers, which form a network on the adventitial surface of cerebral vessels. Several polypeptides are contained within vesicles in the “naked” nerve endings (Fig. 2), including the tachykinins substance P and neurokinin A, together with calcitonin gene-related peptide (CGRP), galanin, and (perhaps) cholecystokinin-8 (see the review by Moskowitz, et al. 1988). Substance P, neurokinin A, and CGRP are vasodilators, and in addition substance P promotes plasma protein extravasation. Release of substance P from pial vessels has been demonstrated in vitro after depolarization of sensory fibers; presumably, this occurs for neurokinin A and CGRP as well (Fig. 3).

Neurogenic vasodilatation develops in facial skin during thermocoagulation of the trigeminal ganglion, and is associated with increased levels of substance P in the jugular vein. Following acute or chronic lower-limb ischemia, venous levels of substance P increase. Levels of CGRP increase in the superior sagittal sinus during electrical stimulation of the trigeminal ganglion. Vasodilatation and plasma protein leakage can be elicited in rat dura mater either by electrical stimulation of the trigeminal ganglion or by the infusion of substance P or neurokinin A. Cutaneous vasodilatation following arterial occlusion is attenuated by 60% in the hind paws of rats after either chronic denervation or capsaicin pretreatment; this response is mimicked by intra-arterial infusion of substance P.

Neuroeffector Influences on Cerebral Blood Flow

Autonomic Influences

The sympathetic and parasympathetic innervation of cerebral vessels has been investigated extensively. Sympathetic nerves play little role in the control of CBF under physiological conditions, during arterial hypotension, hypoxia, or hypercapnia, but may have a protective effect in acute severe hypertension perhaps by promoting vasoconstriction. Only modest reductions in blood flow were observed following electrical stimulation of cervical sympathetic nerves; this can be explained by the constriction primarily of large proximal cerebral arteries.

Parasympathetic nerves contain molecules that promote vasodilatation, such as vasoactive intestinal polypeptide and acetylcholine. Investigation of a parasympathetic influence on CBF has been hampered by the multiplicity of parasympathetic innervation and the lack of a potent and specific vasoactive intestinal polypeptide antagonist, but blockade of cholinergic responses does not influence neurogenic vasodilatation.

Fig. 2. Electron micrographs of cat pial artery. a: Section showing a nerve fascicle containing unmyelinated axons possessing multiple clear vesicles (solid arrows) adjacent to one immunopositive axon (open arrow), × 18,000; bar = 1 μm. b: Section showing a substance P-positive axon and an immunonegative axon in close proximity to vascular smooth muscle. Immunonegative axon contains large granular vesicles (g). Synaptic contacts or junctional complexes were not observed between fibers or terminal axons. Sm = smooth muscle; m = mitochondria; v = vesicles within smooth muscle. × 12,045; bar = 1 μm. (Reprinted from Liu-Chen LY. Liszczak TM. King JC, et al: Immunoelectron microscopic study of substance P-containing fibers in feline cerebral arteries. Brain Res 369:12-20, 1986, with permission.)

Fig. 3. Release of substance P in vitro from nerve endings surrounding bovine pial vessels following superfusion with potassium by calcium-dependent mechanisms. Substance P release was also demonstrable during superfusion with 20 mm potassium or with 1 μM capsaicin. (Reprinted from Moskowitz MA. Brody M. Liu-Chen LY: In vitro release of immunoreactive substance P from putative afferent nerve endings in bovine pia arachnoid. Neuroscience 8:809-814, 1983, with permission.)
Stimulation of parasympathetic projections increases blood flow\textsuperscript{121} by a mechanism independent of brain glucose utilization.\textsuperscript{40} Recent evidence suggests that parasympathetic fibers may modulate the development of collateral blood flow during focal ischemia. The volume of infarcted tissue increased by 30\% to 50\% following middle cerebral artery occlusion after chronic parasympathetic sectioning.\textsuperscript{62} A significantly greater fall in CBF was observed in the denervated hemisphere when perfusion pressure was reduced by controlled hemorrhage. Consistent with the postulation concerning collateral blood flow, no differences in tissue injury were observed between the two sides at 3 to 7 days after 10 minutes of global ischemia.

\textbf{Sensory Influences}

We have recently established that perivascular sensory nerves participate in the regulation of CBF under certain pathological conditions.\textsuperscript{84,103,133} Chronic trigeminal ganglionectomy depletes the ipsilateral circle of Willis of substance P and CGRP, but sympathetic (neuropeptide Y) and parasympathetic (vasoactive intestinal polypeptide) innervation remains intact.\textsuperscript{84} Trigeminal ganglionectomy attenuates the increases in CBF accompanying acute severe hypertension (beyond the limits of autoregulation) and general seizures by approximately 30\% in cats,\textsuperscript{133} and diminishes the extravasation of radiolabeled albumin resulting from disruption of the blood-brain barrier.\textsuperscript{104} Trigeminal sensory fibers limit constrictor responses of pial cortical vessels to topical norepinephrine\textsuperscript{106} and restore constricted vessels more quickly to their resting caliber.\textsuperscript{92,104}

Neurogenic mechanisms, however, are not a major determinant of cerebral autoregulation. Basal CBF is not influenced by deafferentation, nor is there attenuation of the vasodilatory response to hypercapnia.\textsuperscript{84,103} Furthermore, CBF may be reduced at times when the trigeminovascular system is stimulated, such as following subarachnoid hemorrhage.

\textbf{Postischemic Hyperperfusion}

During the reperfusion period following 10 minutes of global cerebral ischemia in cats, postocclusive hyperemia is attenuated by approximately 50\% in cortical gray matter ipsilateral to the side of chronic trigeminal ganglionectomy.\textsuperscript{84,103} Insignificant reductions in CBF develop in cortical white matter or deep gray matter nuclei which, although supplied by the circle of Willis, receive negligible trigeminal innervation. Similarly, sensory denervation does not impair blood flow during the ensuing period of delayed postischemic hyperperfusion (Fig. 4).\textsuperscript{84}

\textbf{Selective Sensory Denervation by Pharmacological Means}

Denervation of perivascular sensory nerves can be accomplished without trigeminal ganglion ablation. Capsaicin, the pungent ingredient in hot peppers, depletes primary sensory afferent neurons of substance P and CGRP by both promoting release and blocking axoplasmic transport (see the review by Buck and Burks\textsuperscript{64}). Topical capsaicin application to a solitary cortical vessel attenuates hyperemia to as great a degree as trigeminal ganglionectomy.\textsuperscript{84} This occurs not only in the vascular territory to which capsaicin is applied directly, but throughout the cortical gray matter of the ipsilateral hemisphere. We presume that this occurs because of the divergence of axon collaterals innervating the cortical vasculature and because all of the axon collaterals from each ganglion cell are affected when capsaicin is applied to a single branch.

\textbf{Pathogenesis}

The attenuation of CBF observed after chronic trigeminal ganglionectomy does not occur following rhizotomy.\textsuperscript{133} Division of the trigeminal root blocks central transmission, but does not result in destruction of the cell body or induce Wallerian degeneration in peripheral axons. Therefore, the neurogenic component of hyperperfusion must be mediated by axon reflex-like mechanisms. The likely stimulus is "real or threatened tissue injury"\textsuperscript{136} and mechanisms that are both dependent and independent of membrane potential changes.\textsuperscript{102} Many of the molecules generated during cerebral ischemia or the reperfusion period, including hydrogen ions, adenosine, ATP, potassium, bradykinin, and arachidonic acid metabolites, are either stimulators or potential...
FIG. 5. Graph showing that pial cortical arterioles (46 to 175 µm) from seven cats dilate in response to topical acetylcholine (ACh), an endothelium-dependent vasodilator, when applied under resting conditions. However, the same dose elicits a vasocostrictor response for the first 60 minutes of reperfusion following 10 minutes of global cerebral ischemia, indicating transient loss of endothelium-dependent relaxing factor (EDRF) reaction. Therefore, non-EDRF vasodilators must mediate the neurogenic component of postischemic hyperperfusion. Data represent the mean ± standard deviation.

Factors of C-fiber activation and may mediate the neurogenic response.

Of the neuropeptides identified within perivascular sensory nerves, substance P and neurokinin A promote vasodilatation through endothelium-dependent mechanisms while CGRP, the most potent of the three, does not require the presence of an intact endothelium. During the early reperfusion period following global cerebral ischemia, cat pial cortical arterioles constrict in response to topical acetylcholine application, an endothelium-dependent vasodilator (Fig. 5). Hence, the ability of sensory nerves to promote vasodilatation at a time when endothelium-dependent relaxing factor reactions are lost (possibly through the generation of free oxygen radicals) indicates that CGRP rather than substance P is likely to be the most important mediator of the neurogenic component of cortical hyperemia, at least in this experimental paradigm.

Functional Significance of Hyperperfusion

Although hyperperfusion is undoubtedly associated with considerable morbidity, before attempts are made to attenuate this phenomenon, researchers should address the issue of whether it is in any way beneficial.

“No-Reflow” Phenomenon

Ames and coworkers originally observed that localized areas of rabbit brain failed to reperfuse after cerebral ischemia, a condition they termed the “no-reflow” phenomenon. It has since been suggested that hyperemia is of importance in re-establishing perfusion after a period of ischemia. However, several studies have failed to show any relationship between the severity of ischemia and the magnitude of hyperemia or between reactive hyperemia and infarct size. Vasodilators such as prostacyclin and calcium channel blockers are of no benefit in improving prognosis after cerebral ischemia, and pathological changes do not correlate well with changes in postischemic CBF. The failure of hypertension to improve neurological recovery after ischemia is further evidence that hyperperfusion is not a significant beneficial determinant of outcome. Indeed, both elevation of blood pressure and surgical revascularization procedures are associated with the increased risk of cerebral edema and hemorrhage. In an experimental study of temporary occlusion of the middle cerebral artery, in which postischemic hyperemia was prevented by hypovolemia, both edema and tissue damage were less than in animals that developed hyperperfusion. Furthermore, preliminary data from our laboratory involving nuclear magnetic resonance perfusion imaging of cat brain perfusion following transient global ischemia has not demonstrated areas of “no reflow” after sensory denervation.

Hypoperfusion

A second potential hazard of therapies designed to attenuate hyperemia is that CBF may also be depressed in unaffected regions or in injured brain at times when there is no excessive perfusion. Hyperemia is generally followed by a second phase of postischemic hypoperfusion, the mechanisms of which are poorly understood. This period may also be a potentially damaging consequence of stroke because a reduction of CBF unmatched by a corresponding lowering of metabolic rate may add a secondary ischemic insult.

Therapeutic Implications

Several therapeutic approaches are suggested by the axonal reflex schema, including blockade of the receptors for the released neuropeptide mediators, blockade of neuropeptide release from nerve fibers, blockade of nerve activation, or accelerated degradation of released neuropeptide. Strategies directed at blockade of axon-like reflexes in brain are still in the early stages of research but, nevertheless, merit discussion.

1. Surgical ablation of the trigeminal nerve or ganglia is unlikely to be of therapeutic relevance. Not only is the resultant neurological deficit unacceptable, but several days must elapse before nerve terminals are depleted of their vasoactive neuropeptides. More selective surgical lesions may not be possible because of the inaccessibility of the neurons and projecting fibers.

R. Macfarlane, et al.
Neuroeffector mechanisms in cerebral hyperperfusion

2. Topical capsaicin application to pial vessels is not practical because of the consequences of neural excitation prior to desensitization and because of the route of administration. Analogs of capsaicin that desensitize but do not excite sensory fibers have greater clinical application, but are still in the early stages of development. 15, 17

3. Local anesthetic agents such as Xylocaine (lidocaine) may be useful because they block voltage-dependent sodium currents and action potentials in sensory fibers. Hence, neuropeptide release would be blocked when mediated by voltage-dependent mechanisms such as depolarization in collateral fibers.

4. Inhibition of action potentials can be accomplished either by blockade of receptors such as the sensory neurons alpha- and gamma-aminobutyric acid-B, or by blockade of voltage-dependent calcium channels by omega-conotoxin. Similar mechanisms may underlie the actions of serotonin-like drugs useful for treating vascular head pain. However, the utility of local anesthetic agents or specific receptor blockers may be suboptimum for two reasons. First, neurotransmitter release is dependent only on partially on membrane potential changes. Second, the mechanisms of axonal depolarization and neurotransmitter release during ischemia are multifactorial.

5. Blockade of neurogenic inflammation by u-opioid compounds may prove relevant to the treatment of hyperemia in brain. Opioid receptors coupled to neurotransmitter release have been postulated to reside on perivascular (heteroreceptor) fibers. Opioids such as lofentanil block neurogenic plasma extravasation in dura by naloxone-sensitizing mechanisms. 32

6. Blockade of neuropeptide vascular receptors may have the greatest potential therapeutic application. Of significance is the demonstration that CGRP is the likely mediator of cortical hyperemia and that CGRP 8-37, a competitive peptide receptor blocker, can antagonize its effect. 34 Although it does not cross the blood-brain barrier well, the demonstration that intravenous CGRP is able to improve the outcome after subarachnoid hemorrhage indicates that this may not be necessary. 38 Tachykinin receptor blockers may prove useful in the control of hyperemia and edema following brain injury.

Conclusions

Release of vasoactive neuropeptides from perivascular nerves, primarily CGRP, is responsible for up to 50% of cortical hyperperfusion. Strategies aimed at blockade of perivascular sensory nerve fibers or their constituent neuropeptides may be of clinical benefit in attenuating hyperemia and cerebral edema in a number of hyperperfusion states.

References


J. Neurosurg. / Volume 75 / December, 1991

851
60. Kägström E, Smith ML, Siesjo BK: Local cerebral blood
77. Lembeck F, Holzer P: Substance P as neurogenic mediator of antidromic vasodilatation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch Pharmacol 310:175–183, 1979
79. Lewis T, Grant R: Observations upon reactive hyperemia in man. Heart 12:73–120, 1925

J. Neurosurg. / Volume 75 / December, 1991


Neuroeffector mechanisms in cerebral hyperperfusion


Manuscript received August 24, 1990.
Accepted in final form April 30, 1991.
This study was supported by Grants NS26361 and NS21558 from the National Institute of Neurological Disorders and Stroke.
Mr. Macfarlane was supported by East Anglian Regional Health Authority.
Address for Drs. Wei and Kontos: Division of Cardiology, Department of Medicine, Medical College of Virginia, Richmond, Virginia 23298.
Address reprint requests to: Michael A. Moskowitz, M.D., Stroke Research Laboratory, Massachusetts General Hospital, Boston, Massachusetts 02114.