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An update on the blood vessel in migraine

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Abstract

Purpose of review—The cranial blood vessel is considered an integral player in the pathophysiology of migraine, but its perceived role has been subject to much discussion and controversy over the years. We will discuss the evolution in our scientific understanding of cranial blood vessels (primarily arteries) in migraine.

Recent findings—Recent developments have clarified the role of cranial blood vessels in the trigemino-vascular system and in cortical spreading depression. An underlying theme is the intimate relation between vascular activity and neural function, and we will emphasize the various roles of the blood vessel that go beyond delivering blood. We conclude that migraine cannot be understood, either from a research or clinical point of view, without an understanding of the vascular derangements that accompany it.

Summary—Migraine is accompanied by significant derangements in vascular function that may represent important targets for investigation and treatment.

Keywords

artery; constriction; cortical spreading depression; dilation; migraine; trigemino-vascular

Introduction

Most physicians have been trained to think of migraine as a ‘vascular headache’, despite the fact that the original ‘vascular hypothesis’ of migraine has been challenged by extensive basic science and clinical evidence. Recent studies have focused to a greater extent on alterations in brain excitability in migraine patients, and debates have characterized migraine in a polarized fashion as either a primarily neural disorder or a primarily vascular disorder. This dichotomy between vascular and neural mechanisms of migraine is simplistic and artificial. Migraine is a complex, multisystem disorder, and blood vessels are quite literally intertwined with all other mediators of migraine pathophysiology. It is important to consider the vessels not as isolated conduits for blood, but rather as complex and heterogeneous components of networks, that are capable of bidirectional signaling with the surrounding parenchyma. In conjunction with perivascular neurons and glial cells, blood vessels are capable of actively detecting and responding to changes in the environment. They are thus ideally placed, both anatomically and physiologically, to exert an influence on migraine.

Vascular physiology in a nutshell

Significant differences in the structure and regulation of blood vessels underlie their different physiological roles, as well as their potential roles in migraine.

Arteries and arterioles consist of an endothelium and basement membrane lining the inner vessel wall (intima), a smooth muscle layer (media), which mediates contraction and dilation, and a connective tissue layer (adventitia) in contact with surrounding tissue. The artery is innervated (primarily by fibers whose cell bodies are outside the brain) in two main layers: within the vessel wall (myoneural synapses), and in the adventitial layer (sensory nerve endings) [1]. Within the brain parenchyma, the adventitial layer is in contact with astrocyte foot processes, and may also be contacted by parenchymal neuronal processes [2]. Capillaries consist of monolayers of endothelial cells with attached pericytes (cells with contractile filaments that may mediate constriction and dilation). Veins lack the media layer and vasomotor innervation of arteries, and serve as capacitance vessels that dilate passively with increased volume. Venous sinuses are formed from layers of dura, and function similarly to veins, but have dense sensory innervation [3,4].

It is important to recognize that blood vessels (especially arteries) are differentially regulated along their length. The large arteries of the circle of Willis are much more densely innervated with sensory and autonomic fibers than more distant branches. And as large surface vessels beget vertical penetrator arteries, there is a reduction in innervation, and most likely a change in locus of control from peripheral to more local neural and astrocytic mechanisms [2,3,5] (Fig. 1).

Arterial motility and regulation

Ultimately, arterial constriction and dilation are mediated by either contraction or relaxation of actin and myosin filaments in smooth muscle cells. A bewildering array of mediators and signaling pathways converge on this common final behavior (Table 1) [3,6,7,8–15]. Constriction or dilation can be induced by arterial contents (blood), the artery wall itself (locally and from a distance), perivascular astrocytes and neurons, and sympathetic, parasympathetic, and sensory nerve terminals in the artery wall. The multilayered regulation is consistent with an obviously critical function.

Localized changes in an artery can be transmitted along its length by intrinsic conduction mechanisms. These conduction mechanisms may involve changes in membrane potential and intracellular calcium as well as purinergic receptor-mediated signaling, in layers of gap junctionally coupled smooth muscle cells or endothelial cells [16]. Conducted dilation has been shown to occur during cortical spreading depression (CSD), the presumed physiological correlate of the migraine aura [17], and in this setting may transmit vascular signals ahead of the slowly propagated wave of neuronal and glial depolarization.

Neurovascular coupling is the process by which neural activity calls up an appropriate blood supply to meet metabolic needs. It arises locally, with the sensation of neural activity by astrocytes, and the transmission of the astrocytic signal to the precapillary arteriole, which then dilates to increase the volume of blood delivered to the active region [18,19]. Measures

of interictal neurovascular coupling appear to be normal in humans with migraine without aura [20•]; however, neurovascular coupling may be disrupted in the wake of the migraine aura [21–23], and as discussed in greater detail below, it is disturbed in both animals and humans during CSD [24–26,27••].

Autoregulation is a homeostatic response of cerebral arteries which keeps cerebral perfusion pressure constant in the face of a range of mean arterial pressures (from ~50 to 150 mmHg). CO₂ reactivity is the perfusion response to alterations in the partial pressure of CO₂ in the blood (dilation to increased pCO₂, constriction to decreased pCO₂). In contrast to neurovascular coupling, which arises locally, autoregulation and CO₂ reactivity are global responses, triggered by carotid chemo- and baroreceptors and possibly by stretch receptors in the cerebral vessels [6,28]. Autoregulation appears to be intact in both humans with aura and animals with CSD. CO₂ reactivity is altered, however. It is increased interictally in migraine patients [29,30], but blunted after aura [23], and after CSD in experimental animals [31].

Sensory and paracrine function

Blood vessels are a focal point for multiple converging functional elements, including processes of sensory and autonomic neurons, astrocytes, and neurons within the brain parenchyma. Considered as a unit, these elements constitute a paracrine organ whose sensory and effector function is not limited to the vessel itself. The classic work of Wolff and Penfield showed that stimulation of cerebral blood vessels causes pain in humans, indicating that they are a primary conduit for intracranial nociceptors [32,33]. Cerebral arteries, dural arteries, and dural sinuses are densely innervated by branches of the trigeminal nerve [3,4]. The nerve fibers are primarily small diameter, unmyelinated nociceptive afferents. However, there are also larger-diameter myelinated fibers [7•], which may serve for mechanosensation. The arterial wall itself may serve as a sensor: vascular smooth muscle cells express transient receptor potential (TRP) family receptors which may be involved in mechanosensation and autoregulation [6].

As detailed in Table 1, endothelial cells, smooth muscle cells, perivascular neuronal fibers, and astrocytes are all capable of release of multiple mediators. Importantly, these mediators not only modulate vascular tone, but also activate receptors on sensory neurons, on surrounding astrocytes, and potentially on surrounding neurons in the brain parenchyma [2,3,19,34,35].

Trigemino-vascular and trigemino-autonomic loops

Trigeminal stimulation, either over cerebral vessels, along the trigeminal nerve, or in the trigeminal ganglion, causes antidromic release of substance P, neurokinins, and CGRP from the afferent terminals. These mediators dilate dural and cortical surface vessels; permeabilize dural vessels leading to plasma protein extravasation; activate perivascular mast cells; and cause further depolarization of the very nerves that released them, creating a positive feedback loop. This feedback can be amplified by activation of parasympathetic efferents, an integrated response referred to as the trigemino-autonomic reflex [3,34]. Both

the trigeminovascular and trigemino-autonomic reflexes can be tested (albeit indirectly) in humans [3,36,37].

Wolff's vascular hypothesis and its downfall

The original 'vascular hypothesis' of Harold Wolff was that the pain of migraine was due to the dilation of pain-sensitive cerebral vessels, and that any preceding aura was due to constriction of these vessels. The hypothesis was based on his [32] and Penfield's [33,38] work showing that cerebral vessels were sensitive to pain, and to his demonstration that vasodilators caused, and vasoconstrictors relieved, headaches [39]. Wolff's ideas have for the most part been refuted. Olesen *et al.* [21] first showed that the pain of migraine with aura actually coincided with hypoperfusion, following a brief hyperperfusion associated with the aura. Further evidence against a simplistic dilation model has come from studies of pharmacologically induced migraine. Most headache-triggering drugs exert a biphasic effect, causing an initial dilation and mild headache in nearly all subjects, and only later (after dilation has stopped) a migraine-like headache in susceptible patients. Interestingly, the initial dilation is of equal size in migraineurs and controls. With headache induced by nitroglycerin (thought to model migraine without aura), Schoonman *et al.* [40•] detected no difference in the diameter of large cerebral and meningeal arteries during headache, despite a significant dilation immediately following nitroglycerin infusion. In addition, not all vasodilators [vasoactive intestinal peptide (VIP) [41] and ethanol [42], for example] cause headache; and not all headache-promoting agents cause vasodilation (sildenafil induces headache but no middle cerebral artery dilation [43,44]). Moreover, not all vasoconstrictors relieve headache, and in fact many vasoconstrictors cause headache: examples are cocaine [45,46], and high or chronic doses of ergots [47,48]. Perhaps most convincingly, reversible cerebral vasoconstriction syndromes and the vasospasm of subarachnoid hemorrhage are intensely painful [49,50]. These experimental and clinical observations show that vasodilation is neither necessary nor sufficient to cause the pain of migraine. However it should be noted that they do not rule out a role for vasoconstriction as an initial trigger for subsequent migraine pain.

Beyond dilation and constriction

Though still popular among nonspecialists, Wolff's vascular hypothesis is a bit of a straw man in the discussion of headache pathophysiology, as the evidence against it is strong, and for years other plausible 'vascular hypotheses' have been available.

The trigemino-vascular/trigemino-autonomic model of headache

The underlying assumption of this robust, experimentally based model is that the vessel (artery or dural sinus), is an agent in the generation and transmission of headache pain, through its sensory, effector, and vasomotor functions. A strength of the trigemino-vascular/trigemino-autonomic (TGV/TA) model is that it directly translates to humans. The same mediators measured in experimental animals can be measured in humans [36,51], though generally surrogate measures are used. Direct electrophysiological recording from brainstem centers is not possible in humans, but indirect measures such as nociceptive blink reflex [52•] and cutaneous allodynia [53,54] can be employed. The systematic testing, in humans,

of substances identified in the rodent trigemino-vascular system has led to significant insights. Calcitonin gene-related peptide (CGRP), a peptide released by trigeminal nerve terminals, was identified over two decades ago as a potential mediator of headache pain [36], and CGRP inhibitors are now poised for clinical use in migraine [55]. Other trigemino-vascular mediators could also be important. Vasoactive intestinal peptide (VIP) and the related pituitary adenylate cyclase activating peptide (PACAP) are released from parasympathetic and trigeminal nerves in cranial blood vessels. Interestingly, VIP failed to elicit migraine-like attacks, even though it caused significant cranial dilation [41]. But PACAP38, the most common form of PACAP, was a potent inducer of migraine-like headaches in patients with migraine without aura [56•]. These paired publications confirm that dilation *per se* may not be the critical step in activation of nociceptive pathways. On an important clinical note, they suggest PACAP inhibitors as migraine therapeutic agents.

Whether insights gained from the TGV/TA model can be extrapolated to all types of migraine is an open question. Most induced migraines (with nitroglycerin [57], CGRP [58], and PACAP [56•], for example) are similar to migraine without aura, even in patients with migraine with aura [57], calling into question whether migraine with aura (or at least the aura portion) is amenable to such study. Moreover, neither NTG nor CGRP induces either aura or migraine in familial hemiplegic migraine, suggesting that these disorders may be biologically distinct, perhaps even from other forms of migraine with aura [59••–61••]. Nevertheless, the systematic testing, in humans, of hypotheses generated using the TGV/TA model is a true example of the power of translational neuroscience, and promises great insights to come.

Other recent insights using the TGV/TA model increase our knowledge of arachidonic acid derivatives (eicosanoids) in the basic mechanisms of migraine. Eicosanoids are products of enzymatic digestion of plasma membrane phospholipids, involved in both conventional neurovascular coupling [62] and the deranged neurovascular coupling that accompanies CSD [63,64]. They are also known mediators of pain and inflammation [65]. Iliff *et al.* [66•] identified epoxyeicosatrienoic acids (EETs) as potential players in the TGV/TA system, by demonstrating the presence of EET synthetic enzymes in trigeminal and sphenopalatine ganglion neurons, and attenuating trigeminally induced cortical hyperemia with an EET antagonist. Maubach *et al.* [67•] identified BGC20–1531, a prostanoid EP4 receptor antagonist, as a potential migraine treatment, demonstrating its ability to bind to the human EP4 receptor, and to antagonize the dilatory effects of PGE2 on human cerebral arteries. Both articles highlight the sometimes neglected role of eicosanoids in migraine, and suggest a targeted investigation of these mechanisms in migraine drug discovery.

Vascular changes during cortical spreading depression

Cortical spreading depression is thought to be the physiological basis of the migraine aura, as hemodynamic events consistent with CSD have been observed during the migraine aura [21,68], and conclusive electrophysiological recordings of CSD have been made in brain injured humans [69,70]. CSD is capable of activating the trigeminal nucleus caudalis [71,72], and is thus inferred to be able to generate the pain of migraine. Finally,

pharmacologically diverse medications used in migraine prophylaxis inhibit CSD [73]. Thus CSD has developed into a model system to study migraine with aura.

It has long been known that stroke causes peri-infarct depolarizations, which are electrophysiologically indistinguishable from CSD [74], and the vasoconstrictor ET-1 is a potent inducer of CSD, likely via ischemia [75]. Nozari *et al.* [76•] used a mouse model of embolic infarction to demonstrate that air, latex microspheres, or cholesterol crystals could all cause CSD. Importantly, they showed a dose response to size and number of emboli, and at the lower end (either size or number) found little or no permanent ischemic damage. From this they inferred that embolization events, subclinical from a stroke point of view, could still cause CSD and thus migraine. The clinical correlation of this work, a reported increased rate of patent foramen ovale (PFO) in migraine, is less robust than previously thought: a population study found no association of migraine and PFO [77]. Moreover the first randomized trial of PFO closure in migraine was negative [78]. But, the physiological proof of principle is valuable, confirming that an ischemic vascular trigger of migraine with aura is possible.

The migraine aura is associated with alterations in neurovascular coupling [21–23], and CSD causes significant derangements in neurovascular coupling in both animal model systems [24–26] and humans [27••]. The CSD wave itself can involve a complete inversion of normal neurovascular coupling [17,27••,79], which can result in tissue hypoxia [27••,80]. Perhaps more relevant to migraine, the hour to 90 minutes following CSD also show disruptions in neurovascular coupling. Two recent studies expand our knowledge of this dysfunction. Piilgaard and Lauritzen [81•] and Chang *et al.* [82•] both show that in the wake of the CSD wave, there is a distinct phase of long lasting mismatch between vascular supply and demand, leading to tissue hypoxia and hemoglobin desaturation. Both also directly show a disruption of neurovascular coupling, which seems to be due to a deficient vascular response. Finally, and counterintuitively (as CSD is thought to silence the cortex), both studies show changes that might favor increased neuronal activity after CSD. Both studies underline the point that neurovascular coupling is a mutable phenomenon, whose characteristics depend on the state of the cortex. They also show that neurovascular coupling is a two-way street: vessels can affect neurons as well as *vice versa*. It is appealing to speculate that the dysregulation of cortical neurovascular function after CSD might help explain altered sensory processing during migraine with aura.

Questions for future research

Migraine is a systemic disorder; the study of migraine is thus obligatorily a study of systems physiology. We can confidently predict that no single reductionistic model system (either in humans or animals) will be sufficient to understand the phenomenon. The way forward likely lies in pooling insights from different model systems. Critical to this is an understanding of what each model tells us, and what it does not, in the light of the vascular physiology we discussed above. Here we raise a few questions for further research, brought up by recent advances.

What kind of vascular changes are we measuring in migraine patients and model systems?

A critical point in the study of vascular changes in migraine is that different techniques look at differently controlled vessels. The best evidence of perfusion changes in humans with migraine comes from techniques (PET, fMRI, scintigraphy or SPECT) that sample changes in the micro-vasculature [21,68,83,84], a compartment structurally and functionally distinct from larger vessels [5,2]. It has been shown that the parenchymal microvascular response and the cortical surface vessel response can be dissociated in rodents [17]. Should we expect the situation to be any different in humans? It is important to understand that a change (or lack thereof) in parenchymal microvessels does not necessarily predict the behavior of larger vessels, and *vice versa*. As the surface vessels are heavily innervated structures that likely transmit pain signals, and the microvessels are in intimate relationship with the neurons that mediate cortical function and dysfunction, the relation of their activity to migraine phenomenology is not merely academic.

On a related note, it should be emphasized that arterial diameter changes related to cortical spreading depression [17] occur in surface vessels that are not reliably accessible to 3T magnetic resonance angiography [40•], even in humans. It should also be noted that the large trunk vessels normally sampled by transcranial Doppler sonography [56•] and magnetic resonance angiography [40•] may not be affected even during massive neurovascular events such as CSD. Again the important message is to know what we are looking at. Moving forward, it would be very helpful to sample surface vessel and parenchymal signal simultaneously in humans during induced and spontaneous migraine. This may be possible using high resolution techniques such as 7T MRI.

Are the vascular changes of spreading depression really relevant to migraine pain?

Cortical spreading depression has shown great utility as a migraine model, but the evidence that it generates migraine pain is of a limited nature, and remains controversial. Different groups have had varying success in eliciting c-fos activation in the trigeminal nucleus caudalis, and it is very difficult to control for other sources of pain in head-restrained animals with cranial surgery [85,71]. Direct electrophysiological evidence of trigeminal activation would be much more conclusive than measurement of immediate early gene activation. Preliminary studies of this nature have recently been presented (Burstein R, 14th Congress of the International Headache Society, 2009).

How can we explain the delay in headache after a vascular disruption or aura?

Nearly all subjects infused with nitroglycerin (or other headache-inducing agents) experience an immediate mild headache which corresponds with cranial and extra-cranial dilation. The migraine-like headache only occurs after a delay of 4–6 h [56•,57,58]. There are also (shorter) delays involved in aura induction in migraine with aura. Elements of the xenon scintigraphy technique used in classic cerebral blood flow studies (likely vascular disruptions, as the technique involved direct infusion of tracer into the carotid circulation) appeared to induce migraine with aura, as events were much more frequent than normal after this procedure [21,22]. Delays to aura were in the range of tens of minutes. Finally, there is a tens-of-minutes delay that typically occurs between aura and the onset of migraine pain. The

mechanisms of these delay phenomena, which could fundamentally alter our understanding of headache induction, are unknown. One might speculate on both local (regenerative release of mediators on the vessel until pain threshold is reached) and networked (trigemino-vascular, brainstem autonomic, and higher cortical) phenomena. Very interestingly, preliminary studies show that trigeminal activation after CSD appears to be subject to a delay of tens of minutes after the wave (Burstein R, 14th Congress of the International Headache Society, 2009). If this is the case, CSD-based models might be used to uncover the basic mechanisms of delay between aura and migraine pain.

Are we neglecting constriction and hypoperfusion?

It is interesting how much emphasis is placed on craniovascular dilation or hyperperfusion, when strong experimental evidence in both humans and animals shows constriction or hypoperfusion to be equally prevalent [17,21,27•,68,79,82•,84]. Constriction is at least as plausible as dilation as a pain trigger; in fact CGRP and nitric oxide are released in response to constriction [3]. Of particular interest is the highly replicable hypoperfusion in humans after the migraine aura, and in animals after CSD [21,68,81•,82•]. Recent evidence [81•,82•] emphasizes the long-known disruption of neurovascular coupling after CSD, and suggests a mismatch in metabolic demand and supply. Such mismatches are potent triggers of pain in the periphery – the best-known and most extreme example is angina. Could the post-aura hypoperfusion be a pain stimulus in itself?

What can we learn from the ‘pure’ vasculopathies?

Much appropriate emphasis has been placed on the mutations that confer familial hemiplegic migraine, two of which (CACNA1A and SCN1A) code for neuronal ion channels, and are thought to increase neuronal excitability [86,87]. However, there are disorders whose phenotype includes migraine that involve exclusively vascular disease. The most prominent of these is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukodystrophy (CADASIL; *NOTCH3* mutation). Two others are retinal vasculopathy with cerebral leukodystrophy (RVCL; *TREX1* mutation) and hereditary infantile hemiparesis with retinal arterial tortuosity and leukoencephaly (HIHRATL; *COL4A1* mutation) (reviewed in [88]). The mutations are diverse but a common theme of all three disorders is a structurally and functionally abnormal cerebral vasculature. Given the demonstrated ability of the endogenous vascular mediator endothelin-1 to cause vasospasm and CSD [75], a common unifying hypothesis would be that these disorders share a tendency toward vasospasm which could both induce CSD and directly cause cranial pain. In this light it is interesting to note that CADASIL transgenic mouse arteries have reduced flow-induced dilation, and increased pressure-induced myogenic tone, suggestive of a tendency toward constriction [89]. Focused physiological study of human mutation carriers in these ‘pure’ vasculopathies, and generation of more mouse models, could reveal a great deal about potential vascular mechanisms of headache.

Conclusion

The craniocerebral blood vessel is not just a carrier of blood: its intrinsic sensory and secretory abilities, as well as its inextricable association with perivascular nerves and

astrocytes, make it an integral part of a sensory and effector network. It is multiply and variably regulated along its length, and it is bidirectionally linked with the brain in the parenchyma (through neurovascular coupling mechanisms) and in the periphery (through trigeminal and autonomic nerves). Migraine, especially migraine with aura, is consistently linked with micro or macrovascular changes during the attack. The idea that simple dilation or constriction can explain migraine pain is simplistic, but the rejection of the vessel as an agent of migraine is equally simplistic. Recent work on two key models of migraine – the trigemino-vascular model and cortical spreading depression – bears this out. Alterations in vascular function may or may not be the first derangement in a migraine attack: we would argue that the initial step can vary, with several possible pathways that lead to the generation of pain. But migraine cannot be understood without a clear understanding of the dynamic role of the blood vessel in its pathogenesis.

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References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Figure 1.

The varied regulation of the cerebral artery

Schematic shows a cortical surface artery, with its penetrator branches and arterioles in the cortex itself. The surface vessel is heavily innervated by sensory fibers from the trigeminal ganglion (TG), parasympathetic fibers from the sphenopalatine and otic ganglia (SPG/OG), and sympathetic fibers from the superior cervical ganglion (SCG). Peripheral innervation trails off as arteries enter the cortex, and regulation switches primarily to more local mechanisms. Inset: the 'neurovascular unit' consists of astrocytes which contact local neurons as well as arterioles (via their end-feet). Neurovascular coupling is mediated by the astrocyte, which transduces signals from neural activity (glutamate, K^+) either directly or indirectly onto the vessel, causing dilation and increased blood flow. Interneurons have been shown to contact vessels directly, though the significance of these contacts is debated. Finally, ascending projections from brainstem nuclei can modulate cortical arterial diameter (note that they can also do this through effects on the trigeminal, parasympathetic, and sympathetic nerves that contact surface vessels). The differential regulation of cerebral vessels is highly relevant to migraine: cortical surface vessels are likely conduits for migraine-associated pain; and parenchymal microvessels are in close apposition to the neurons involved in cortical migraine phenomena. 5HT, serotonin; ACh, acetylcholine; CGRP, calcitonin gene-related peptide; GABA, g-amino butyric acid; glu, glutamate; NA, norepinephrine; NKA, neurokinin A; NOS, nitric oxide synthase; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase activating peptide; PNS, peripheral nervous system;

SOM, somatostatin; SP, substance P; VIP, vasoactive intestinal peptide. Reproduced with permission from [2].

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Table 1

The regulators of cerebral arterial function (a partial list)

Mediator	Effector(s)	Source/location	Comments
Constriction			
Ca ⁺⁺	L-type Ca ⁺⁺ channel; ryanodine receptor	Extracellular; endoplasmic reticulum	Ca ⁺⁺ entry, and release from internal stores mediates excitation–contraction coupling in smooth muscle cells.
Membrane voltage (Vm)	L-type Ca ⁺⁺ channel	Perivascular nerves, astrocyte foot processes. Endothelium?	Depolarization of smooth muscle cells causes constriction via Ca ⁺⁺ -mediated mechanisms.
Endothelin-1 (ET-1) ^a	Endothelin-A receptor (ETA-R)	Endothelium, brain parenchyma. Perivascular nerves?	Relevant to intrinsic tone, also activated by tissue injury. Activation of ETA-R increases [Ca ⁺⁺] _i via G-protein coupled mechanisms.
Norepinephrine (NE) ^a (NPY, ATP co-released) ^a	α-1 adrenoreceptor, (NE); P2X purinergic receptor (ATP)	Sympathetic nerves (superior cervical ganglion)	Increases in intracellular Ca ⁺⁺ via phospholipase C (NE, NPY); Na ⁺ and Ca ⁺⁺ entry (ATP).
Arachidonic acid (AA) derivatives (eicosanoids)	20-HETE ^a (via epoxigenase), thromboxane A ₂ ^a (via cyclooxygenase)	Astrocytes (generate AA via phospholipase A ₂)	AA diffuses to vascular smooth muscle cell (VSMC) and is converted to 20-HETE. 20-HETE constricts by inhibiting VSMC BK _{Ca} ⁺⁺ channels, activating L-type Ca ⁺⁺ channels, and inhibiting NO production.
Serotonin (5-HT) ^a	5HT1b/d/f (to G _{i/o} proteins) 5HT2a (to G _{q/11} proteins)	Platelets, mast cells, raphe nuclei, sympathetic nerves?	5HT1b/d activity may constrict via AA derivatives. 5HT2a activity constricts via [Ca ⁺⁺] _i elevation.
Transmural pressure	Transient receptor potential (TRP) channels via cation entry?	Endothelium? Vascular smooth muscle cell (VSMC)?	Stretch results in depolarization, constriction.
Hemoglobin (Hb) ^{a,b} K ⁺ ^{a,b}	Reactive oxygen species Vm	Subarachnoid hemorrhage Spreading depression, stroke, tissue injury (generally K ⁺ above 20 mM)	Hb scavenges NO, impeding dilation. Membrane depolarization opens voltage gated Ca ⁺⁺ channels.
O ₂ ^{a,b}	Superoxide anion (O ₂ ⁻) ?	Hyperoxia	O ₂ ⁻ generated in hyperoxic

Mediator	Effector(s)	Source/location	Comments
Dilation			conditions may inactivate NO.
K^{+a}	K_{Ca}^{++} , K_{ATP} , K_{IR} , $K_{(v)}$	Neural, astrocytic activity, other mediators (see below)	K^{+} efflux hyperpolarizes VSMC membrane, allows dilation.
V_m	Endothelium-derived hyperpolarizing factor (EDHF) (likely H_2O_2)	Endothelial cells	EDHF activates K_{Ca}^{++} channels.
Nitric oxide (NO) ^a	cGMP, myosin light chain phosphatase	Endothelial cells, parasympathetic nerves (from pterygopalatine ganglion, otic ganglion)	NO inactivates myosin light chain kinase via guanylate cyclase and myosin light chain phosphatase.
Acetylcholine (ACh) ^a	NO, inhibition of NE release	Parasympathetic nerves	Dilation via NO and inhibition of NE constriction.
VIP, PACAP ^a	PAC1, VPAC1,2 receptors	Parasympathetic nerves	Dilation via NO.
Transmural pressure	K_{Ca}^{++} , K_{ATP} , Cl^{-} channels	Endothelium? VSMC?	Stretch results in hyperpolarization, dilation.
Adenosine ^a	Adenosine A2A receptor, L-type Ca^{++} channel; GIRK channel	Conversion from ATP, other purines extracellularly and intracellularly.	A2A receptor reduces L-type Ca^{++} channel activity via tyrosine phosphatase; adenosine can activate GIRK channels, cause hyperpolarization.
Serotonin (5-HT) ^a	5HT1b/d/f (to $G_{i/o}$ proteins)	Platelets, mast cells raphe nuclei?	5HT1b/d activity dilates via NO, EDHF. Most studies show that the net 5HT1b/d effect is constriction (see above).
Calcitonin gene-related peptide (CGRP) ^a	CRLR/RAMP1	Trigeminal nerves	CGRP binding activates K_{ATP} channel, hyperpolarizes VSMC (NO production also increased).
Substance P (SP) ^a , Neurokinin A (NKA) ^a	Neurokinin 1 (NK1) receptor	Trigeminal nerves	NK1 activation increases NO production.
Arachidonic acid (AA) derivatives (eicosanoids)	PGE2 ^a	Astrocyte (generates AA via phospholipase A2)	Activation of K^{+} channels hyperpolarizes VSMC (may also increase NO production).
Glutamate ^a	Metabotropic glutamate receptor (mGluR); AA derivatives.	Astrocyte	Activation of mGluR on astrocyte increases AA derivative (EET) release.

	Mediator	Effector(s)	Source/location	Comments
	Bradykinin ^a	K _{Ca} ⁺⁺ activation, NO, EDHF	Venular endothelium	K ⁺ efflux, EDHF hyperpolarizes VSMC, NO relaxes.
	Histamine ^a	H1, H2 receptors	Mast cells, endothelial cells, smooth muscle cells, glia?	H1 effects via G-protein and phospholipase C; H2 effects via myosin light chain kinase.
	Estradiol ^a (progesterone) ^a	NO, EDHF, BK _{Ca} ⁺⁺	Circulation, brain parenchyma?	K ⁺ efflux, EDHF hyperpolarizes VSMC, NO relaxes.
	Angiotensin II	AT1,2 receptors	Circulation	AT receptor activation increases VSMC Ca ⁺⁺ levels favoring constriction
	CO ₂	Multiple, including acid sensing ion channels	Circulation	Dilation via cholinergic mechanisms.
Sensation				
Nociceptive	H ⁺ , K ⁺ , CGRP, stretch?, cytokines? others?	TRPV1 receptor, CRLR/RAMP1, others?	Trigeminal ganglion	Trigeminal afferent activation increases TNC activity, also antidromic release (trigeminovascular reflex).
Mechanical	Constriction, dilation, traction, perfusion pressure	Stretch receptors (TRP family?)	Trigeminal ganglion, vessel wall	May form component of nociceptive response, also response to blood pressure (autoregulation).

20-HETE, 20 hydroxyeicosatetraenoic acid; ATP, adenosine triphosphate; BK_{Ca}⁺⁺, large conductance calcium activated potassium channel; [Ca⁺⁺]_i, intracellular calcium; cGMP, cyclic guanosine monophosphate; CRLR, calcitonin receptor-like receptor; GIRK, G-protein coupled, inwardly rectifying potassium channel; K_(v), voltage gated potassium channel; K_{ATP}, ATP-sensitive potassium channel; K_{Ca}⁺⁺, calcium activated potassium channel; K_{IR}, inwardly rectifying potassium channel; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase activated peptide; RAMP1, receptor activity modifying protein 1; TRP, transient receptor potential family of receptors; TRPV1, transient receptor potential (vanilloid 1); VIP, vasoactive intestinal peptide. Data from [3,6,7*, 8–15]. Not all references could be included for reasons of space.

^a A mediator or effector which has effects on vessel, perivascular nerves, astrocytes, or parenchymal neurons beyond simple constriction or dilation. See text for further detail.

^b Pathological.