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Neurovascular coupling: Motive unknown

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Abstract

It has been known for more than century that increases in neural activity in the brain drive changes in local blood flow, known as neurovascular coupling. The colloquial explanation for these increases in blood flow (referred to as functional hyperemia) in the brain is that they serve to supply the needs of metabolically active neurons. However, there is an large body of evidence that is inconsistent with this idea. In most cases, baseline blood flow is adequate to supply even elevated neural activity. Neurovascular coupling is irregular, absent, or inverted in many brain regions, behavioral states, and conditions. Increases in respiration can generate increases in brain oxygenation independently of flow changes. Simulations have shown that areas with low blood flow are inescapable and cannot be removed by functional hyperemia given the architecture of the cerebral vasculature. What physiological purpose might neurovascular coupling serve? Here, we discuss potential alternative functions of neurovascular coupling. It may serve supply oxygen for neuromodulator synthesis, to regulate cerebral temperature, signal to neurons, stabilize and optimize the cerebral vascular structure, deal with the non-Newtonian nature of blood, or drive the production and circulation of cerebrospinal fluid around and through the brain via arterial dilations. Understanding the 'why' of neurovascular coupling is an important goal that give insight into the pathologies caused by cerebrovascular disfunction.

Introduction

Like all energy demanding organs, the brain is highly vascularized. When presented with a sensory stimulus or cognitive task, increases in neural activity in many brain regions are accompanied by local dilation of arterioles and other microvessels, increasing local blood flow, volume and oxygenation. The increase in blood flow in response to increased neural activity (known as functional hyperemia) is controlled by a multitude of different signaling pathways via neurovascular coupling (reviewed in [1,2]). These vascular changes can be monitored non-invasively in humans and other species, with techniques (like BOLD fMRI) that are cornerstones in modern neuroscience [3,4]. Chronic disruptions of neurovascular coupling have adverse health effects on the brain. Stress affects neurovascular coupling [5,6], and many neurodegenerative diseases are marked by vascular dysfunction [7]. There is evidence suggesting that neurovascular dysfunctions plays a role in autism [8] and other

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mental disorders [8–10]. It is clear that functional hyperemia has an important physiological role to play, and that its disruption has adverse impacts on brain function.

What is not so clear is the *purpose* of functional hyperemia. Functional hyperemia is often described as being necessary to supply the metabolic needs of neurons. However, in most cases the increase in blood flow elicited by sensory stimulation and neural activity is more than what is required for supplying the more active neurons, resulting in an increase in blood and tissue oxygenation that serves as the contrast mechanism in BOLD fMRI [11–13]. Moreover, even the baseline levels of blood flow are more than adequate to supply oxygen to neurons with elevated levels of activity [14]. The finding of an oversupply of oxygen in response to elevated neural activity did not make sense from the point of view of energetics (but see below for discussion of the potential effect of heterogeneities in flow), but was useful, so such concerns fell by the wayside, though the conundrum has been noted many [14,15]. It is also important to keep in mind that the blood flow increases during sleep are substantially larger than anything in the awake brain [16,17], so whatever purpose functional hyperemia serves, it is operating at an elevated level during sleep.

This review will not provide a detailed discussion of mechanisms mediating neural and glial control of the vasculature, for which we direct the reader elsewhere [2]. Rather, it addresses what alternative roles functional hyperemia might have other than delivering oxygen to support the metabolic needs of active neurons. The observation that the functional hyperemia does not ‘make sense’ is not a new one, as many investigators in the past decades have noted the lack of obvious purpose for functional hyperemia (see [14,18]) and the potential for non-canonical roles of functional hyperemia [19]. This review does not provide a resolution to the role of neurovascular coupling and functional hyperemia, but will provide a discussion of the possibilities of the physiological function of this blood flow dynamics in the brain. Some hypotheses presented are more plausible than others, and the actual purpose may not be among those presented here.

Neurovascular coupling is inverted or absent in many brain areas and is not reflective of metabolic activity

The purpose of functional hyperemia has been frequently described as being required to supply the increased metabolic needs of neurons. However, there is a long list of areas and conditions where blood flow does not track neural activity (Fig. 1), and neurovascular coupling can differ among brain regions [20]. Nociceptive stimulation produces increases in neural activity in the caudate putamen, but a profound decrease in blood volume [21,22]. During locomotion in rodents, neural activity goes up in frontal and motor areas, but blood flow does not [23–25]. Similar dynamics may be at play in the hippocampus [26]. In the olfactory bulb, weak sensory stimuli can drive nonspecific blood flow outside the activated area [27], and anticipation of a sensory stimulus can generate arterial dilations without matching neural activity in the visual cortex of primates [28]. During limb stimulation, in the ipsilateral somatosensory cortex, metabolic activity and blood flow are anticorrelated [29]. In the hypothalamus, neurovascular coupling can be inverted by salt loading [30]. In primates, many studies have shown that spatial attention causes large, localized BOLD

signal increases that are not matched by increases in neural activity [31]. Vasodilation itself is not necessarily required to drive increases in brain oxygenation. Cerebral oxygenation can be elevated simply by increasing the breathing rate, as blood is not saturated with oxygen at baseline in rodents [25], so functional hyperemia is not required to raise oxygen levels. If functional hyperemia is necessary to supply oxygen to active neurons, it is odd that the link between neural activity and blood flow is so weak.

If the metabolic demand of neurons was paramount, we might expect metabolic signals from neurons to dominate the control of the cerebral vasculature. This does not seem to be the case. Though potassium released from active neurons can drive vasodilation [32], nitric oxide (NO) seems to be the dominant (but far from only) regulator of the cerebral vasculature [33]. Opto- or chemogenetic stimulation of nitric oxide generating neurons (which are a small subset of interneurons [34,35]) can drive large arterial dilations and flow increases with little to no overall change in neural activity [36–38], showing that blood flow regulation could function largely independent of the metabolic demand. Neural-evoked changes in NO production have similar temporal dynamics as K+ increases, so NO is not likely be used as a ‘feed-forward’ control. Intriguingly, breath-holding animals, such as crocodiles (which can hold their breath for tens of minutes to hours), show similar BOLD responses as mammals in response to sensory stimulation [39]. Because of this, it is hard to attribute the increase blood flow to meeting a metabolic oxygen demand.

Baseline blood flow is more than adequate to supported elevated neural activity

The electrical gradients of neurons are energetically expensive to maintain, and require a large portion of the brain’s metabolic budget [40]. While lower levels of blood oxygen tension (like those at high altitude), are associated with decrease in cognitive performance, this is not due metabolic impairment in the brain. Early studies of brain metabolism showed that ATP/ADP ratios did not fall unless arterial oxygen tension was very low (~20 mmHg, comparable to what one would achieve climbing Mount Everest without supplemental oxygen) [41], consistent with the observation that the respiratory enzymes in mitochondria are saturated at extremely low oxygen tensions (in the range of 2 mmHg) [42]. As the normal tension of oxygen in brain tissue (>5 mmHg) is able to saturate mitochondrial respiratory enzymes, bottom-up and top down measurements agree that under normal conditions the brain is oversupplied with oxygen. Simulations of oxygen transfer combined with radiolabeled oxygen studies in humans have supported the idea that resting blood flow is more than adequate to supply oxygen to the brain [14].

In addition to these findings, several pharmacological findings support the idea that the baseline flow of blood may already be more than enough to supply the brain with oxygen. Indomethacin, a commonly prescribed anti-inflammatory drug which inhibits the synthesis of prostaglandins, decreases cerebral blood flow 30–40% [43], may actually increase metabolic rate in the brain [44], but produces no significant cognitive effects [45]. The amount of caffeine in a single cup of coffee produces decreases of ~30% in cerebral blood flow, with little to no change in metabolic rate [46,47]. If the brain were operating at its

metabolic limits, a cup of coffee in the mountains would be catastrophic. Since the brain has limited ability to compensate for the flow effects of caffeine [48], it is not likely that chronic caffeine use drives a desensitization that results in baseline blood flow returning to normal in habitual coffee drinkers. These pharmacologically-mediated decreases in flow are large enough that any increase due to functional hyperemia in the drug condition will be below pre-drug baseline. Whatever blood is supplying, oxygen or some other metabolite, the baseline flow of blood seems more than adequate to meet it.

Neuromodulator synthesis may be oxygen limited

However, there may be other demanding roles for oxygen other than supporting cellular respiration. The synthesis of many small signaling molecules requires oxygen. Interestingly, the synthesis pathways of many neuromodulators (such as acetylcholine [49,50] and norepinephrine [51]) is oxygen-limited [52], with the synthesizing enzymes having disassociation constants for oxygen in the range of tens of mmHg in some cases [42]. This means that under some conditions within the range of normal physiology (e.g. high altitude), the synthesis of neuromodulators may be impaired (and disruption of neuromodulator levels may account for decreased mental functioning at high altitude, for example). Functional hyperemia might serve increase oxygen levels to support neuromodulator synthesis. This possibility could be testable given the recent advances in fluorescent biosensors [53].
An important consideration is the turnover rate for the neuromodulators whose synthesis is dependent on oxygen [54]. Some are rapidly broken down and resynthesized giving them an effective half-life of minutes (like acetylcholine [55]), others show lower rates of breakdown and synthesis, giving them a half-life of hours (such as norepinephrine [56]). The shorter duration blood flow increases associated with neurovascular coupling in the awake brain may help replenish the shorter-lived neuromodulators, while the sustained increases in the blood supply during sleep may supply the oxygen needed for synthesis of the neuromodulators with less rapid cycling.

Oxygen also plays a role in the breakdown of NO, which will impact neural activity. In addition to its role as a vasodilator, NO affects neural excitability via second messengers (like cGMP)[57,58]. Interestingly, NO lifetime in the brain tissue is inversely related to oxygen concentration [59], so increases in oxygen mediated by functional hyperemia (as well as decreases in oxygenation mediated by inverted neurovascular coupling) might provide a signal affecting neural excitability.

Delivery/removal of chemicals other than oxygen

Besides oxygen, the cerebral blood flow brings in glucose and removes CO_2. CO_2 is a powerful vasodilator (mainly via changes in brain pH, but also through direct action [2,60]), but the dynamics of these changes will be on the time scale of minutes [61], and not something that brief hyperemic responses can deal with effectively. The brain is only able to extract a small fraction of the glucose from the blood [62], functional hyperemia persists during hypo/hyperglycemia [63] and after hemodilution [64], so it seems unlikely that the role for functional hyperemia is to supply glucose It could be that other signaling factors in the plasma which are taken up by the brain [65,66] are limited by flow and functional

hyperemia serves to supply them specifically to activated regions. As these signals come from the muscles and other organs, neurovascular coupling may provide an interoceptive mechanism for organs to chemically signal to specific brain regions that are active.

Could functional hyperemia serve to reduce stalling and capillary flow heterogeneity?

From the first observations blood flow in the brain at single capillary level, it has been observed that the flow through individual capillaries was heterogenous, and the flow within a single capillary could undergo stalls and flow reversals [67–70]. Subsequent work has implicated leukocytes with generating these stalls and has correlated the frequency of and susceptibility to stalls with neurodegeneration [71–73]. These stalls are thought to be related to poor perfusion in small areas and may cause a sudden drop of tissue oxygenation near the capillary [74]. One possible role of functional hyperemia might be to ‘unplug’ these stalled capillaries by providing an increase in pressure that breaks the adhesion of the leukocyte to the endothelium.

It has been posited that increases in blood flow serve to supply oxygen to poorly perfused, low flow regions, and the oversupply of blood and oxygen is a side effect of this attempt to prevent hypoxia in these poorly perfused areas [18,75]. Recently, the impact of increasing blood flow on these low flow regions has been explored using simulations [76]. Surprisingly, these simulations showed that given the geometry of the cerebral vasculature, low flow regions are an inescapable consequence of the architecture of the cerebral vasculatures, and increases in blood flow, whether locally or globally, will serve only to move the location of the low-blood flow regions, not eliminate them [76]. This effect is due to the fact that blood flows through the capillary beds from high pressure regions (penetrating arterioles) to low pressure regions (ascending venules). In the cortex, penetrating arterioles and ascending venules are interspersed [77–79], and the pressure gradient in the capillaries goes down between these two vessel types. However, there will be regions (roughly equidistant from pairs of arterioles or venules) where the pressure gradient through the capillary bed is minimal. Given the anatomy of the cerebral vasculature, increases flow in any number of vessels does not remove the low flow region, it merely moves them. These simulations strongly challenge the conventional narrative of neurovascular coupling, as there will always be low flow regions (though reducing the resistance of the vascular network will increase the net flow). Low flow regions could be moved around by fluctuations in flow (e.g. non-neuronally-driven vasomotion [80,81]), so there is no clear need for overall flow increases.

Temperature homeostasis

Changes in the flow of blood to the brain could serve a thermoregulatory role [82]. Under sedentary conditions at non-extreme temperatures, the brain will tend to heat itself slightly above the core temperature [83], though physical exertion can cause the core to become hotter than the brain. Brain areas that are metabolically active will generate heat, and the increased flow could serve to homogenize temperature gradients across the brain and with the core. Many ungulates possess a heat exchanging vascular structure at the skull base known as the carotid rete[84]. Arterial blood destined for the brain passes through a

cavernous sinus filled with of venous blood leaving the brain just prior to it entering the circle of Willis. When the core temperature is high, the carotid rete serves a countercurrent heat exchanger, cooling the blood coming from the core before it enters the brain, at the expense of some wasted oxygen. Humans, rodents, and many other animals lack a carotid rete. Using MRI, there are reports of brain cooling by increased blood flow following visual stimulation in humans [85]. In rodents, cooling the body reduces the amplitude of functional hyperemia [86]. Brain temperature decrease causes drops in resting capillary blood flow, capillary PO_2, hemoglobin saturation and tissue PO_2 in the mice olfactory bulb and somatosensory cortex [87]. Mouse brain temperatures are not substantially increased by exercise [88], but stress and torpor can respectively cause large increases and decreases in rodents [89,90]. The drop in brain temperature does not block spatial learning in rodents [91], but oxygenation and neural activity are affected by temperature [87,92–95]. The sensitivity of a mouse, crocodile and cow to temperature fluctuations should be very different, but neurovascular coupling is present in all of them.

Role in CSF circulation and production

The movement of cerebrospinal fluid through and around the brain (via the glymphatic system) plays an important role in the removal of waste (particularly during sleep), and failure of this movement is thought to be a leading cause of neurodegenerative diseases [96]. Experiments in rodents have shown that periodic arterial vasodilation (whether sensory-evoked or spontaneous), can help remove a tracer from the area faster than without these dilations [97], and the large vascular changes accompanying awakening drive CSF movement [98]. Simulations have shown that slow arterial dilations are effective at moving CSF in and out of the para-arterial space surrounding penetrating arteries [99] and through the porous brain tissue [100], both of which would facilitate the removal of waste from the brain. During sleep, the extracellular space of the of the brain increases in size, making the brain more porous and increasing the inflow of dye into the brain [101]. This increase in porosity, combined with the enormous arterial dilations during sleep [16] would facilitate fluid flow and help clear waste from the brain [96].

Increases in blood flow may play a role in locally generating CSF. Textbook descriptions of CSF production focus on its generation in the ventricles by the choroid plexus [102]. However, CSF production continues when the choroid plexus is excised, and there is evidence that CSF is produced by the capillaries and other vessels in the brain [102]. Under resting conditions, it is thought that capillaries have minimal permeability to ions, water would be largely prevented from crossing the blood brain barrier (BBB) by osmotic forces [103], unless the BBB becomes more permeable (transiently and locally) to ions. Many molecules involved in neurovascular coupling increase permeability of endothelial cells to ions, such as adenosine [104], serotonin [105], and histamine [106]. Dilation of arteries and other vessels would increase the absolute pressure in the capillaries relative to the brain, and thus increase effective pressure gradient between the cerebral vasculature and the brain. Pairing this dilation with appropriate increases in BBB permeability to ions would cause a secretion of CSF by the vasculature into a localized brain area. Functional hyperemia would allow this to take place on a spatially and temporally restricted area, and be under the control of local neural activity. A slight increase in CSF production in one area would

result in a pressure gradient in the tissue, and convective flow of fluid (and any solutes) away from this brain area. This could be important as small pressure gradients in the brain could drive substantial convection of fluid in the brain [107]. If functional hyperemia drives CSF movement and/or production that transports brain waste out of the brain, this could explain the linkage between the failure of neurovascular coupling and neurodegeneration [108,109]. However, measurements of CSF production, particularly on this scale are experimentally challenging.

Dynamic vascular signaling to neurons – the hemo-neural hypothesis

One possible function of the blood flow increase might serve is as a signal to neurons, known as the hemo-neuro hypothesis [19,110]. In this hypothesis, some factor(s) (either directly or indirectly caused by vasodilation) serves as a signal to regulate excitably or activity in neurons. As blood flow increases are relatively slow (lasting a few seconds) and spatially broad, they may provide a distinct spatiotemporal pattern of signaling from synaptic interactions. Some potential factors include NO, oxygen, or mechanical signaling, and there is some evidence for each of these.

Vasodilation causes a local increase in hemoglobin and oxygen concentrations, which will substantially increases the degradation rate of nitric oxide, with the result that vasodilation may causes a drop in NO below baseline levels [111]. As nitric oxide affects the excitability of neurons as well via cGMP pathways [57,58], these changes in blood volume could impact neural activity [112], providing a potential mechanism for hemo-neural signaling. There is a precedence for this as in vitro, nitric oxide produced by endothelia cells can modulate the excitability of neurons [113] (note that due to the lack of perfusion and higher oxygen levels in slice preparations, in vitro NO dynamics will differ from those in vivo). Changes in oxygen levels may directly modulate neural excitability via direct actions on ion channels found in the brain [114,115].

One potential pathway of the signaling might be via mechanical forces. In slice preparation where a penetrating arteries has been cannulated to recreate the mechanical forces produced by flowing blood, changes in flow cause changes in interneuron spiking [116]. Astrocytes are sensitive to the mechanical forces generated by arterial vasodilations and constrictions [117]. Elastography studies has suggested that stiffening occurs in regions of vasodilation [118]. There is evidence that the mechanical restriction of arteries (due to the viscoelasticity of the brain tissue that surrounds it) constrains the dilation of arterioles in the brain [119] and the dilations of penetrating arterioles deform the brain tissue [99]. Given the diversity of mechanosensory mechanisms present in cells, the mechanical effects of vasodilation is a plausible signaling mechanism.

Non-Newtonian nature of blood and vascular network stabilization

Blood is a suspension of red blood cells (RBCs) in plasma, which is substantially more viscous than water. When treated as a continuum, the behavior of this suspension can be approximated with vessel-diameter dependent viscosity, with the effective viscosity rising with decreasing vessel diameter [120]. However, this continuum model breaks down in

smaller scale vessels, as the RBCs are substantially more viscous than the plasma, as blood flow in capillaries behaves differently than a pure fluid [121]. Microfluidic models with droplets of different viscosity exhibit stochastic oscillations in flow [122], as does blood when pushed through microfluidic channels of similar size as capillaries [123]. Simulations have revealed similar red blood cells jamming dynamics [124]. These oscillatory behaviors of red blood cells in plasma would never arise in Newtonian fluid (no matter how viscous), and are substantial enough deviations from the continuum approximations that they call their use in modeling flow through vessels smaller than arterioles into question. It could be that this non-Newtonian behavior of blood requires something like functional hyperemia to avoid RBC jamming or large oscillations in flow [125].

Another possible role for functional hyperemia is to send mechanical signals to the vasculature that are used as feedback in stabilizing the network. Endothelial cells can respond to mechanical forces, and use mechanical cues like the shear stress exerted by flowing blood to guide the assembly the brain vasculature [126,127]. While the vasculature is largely stable in the adult [128–130], it is likely that there are homeostatic stabilizing processes maintaining this structure that are guided by mechanical forces exerted by flowing blood. Flow increases cause higher shear stresses on the walls. Theoretical studies have suggested that local (non-global) fluctuations in flow, like those driven by functional hyperemia, could stabilize anastomoses (‘loops’) in vascular networks using local sensing of flow [131], like the shear stress changes generated by increased flow. These loops are found at both the capillary [132] and arteriole levels [78,133] and endow the network with some robustness against occlusion. Flow changes by guided by neural activity could serve to sculpt this process.

Concluding remarks

The brain’s metabolism operates with a substantial safety margin in its oxygen supply, yet apparently ‘useless’ blood flow increases frequently follow increases in neural activity [134]. There are several, non-exclusive possibilities for the function of neurovascular coupling (Fig. 2) (see Outstanding Questions), and given the heterogeneity in neurovascular coupling [20] and vascular structure [79] across the brain, neurovascular coupling may serve different roles in different places. Comparative approaches that harness differences and commonalities in neurovascular physiology across species may be very enlightening [135]. Addressing the true physiological function(s) of neurovascular coupling will help explain how its disfunction contributes to the development neurodegenerative diseases and mental disorders [7], and will give insight into its variability across brain regions and conditions [20].

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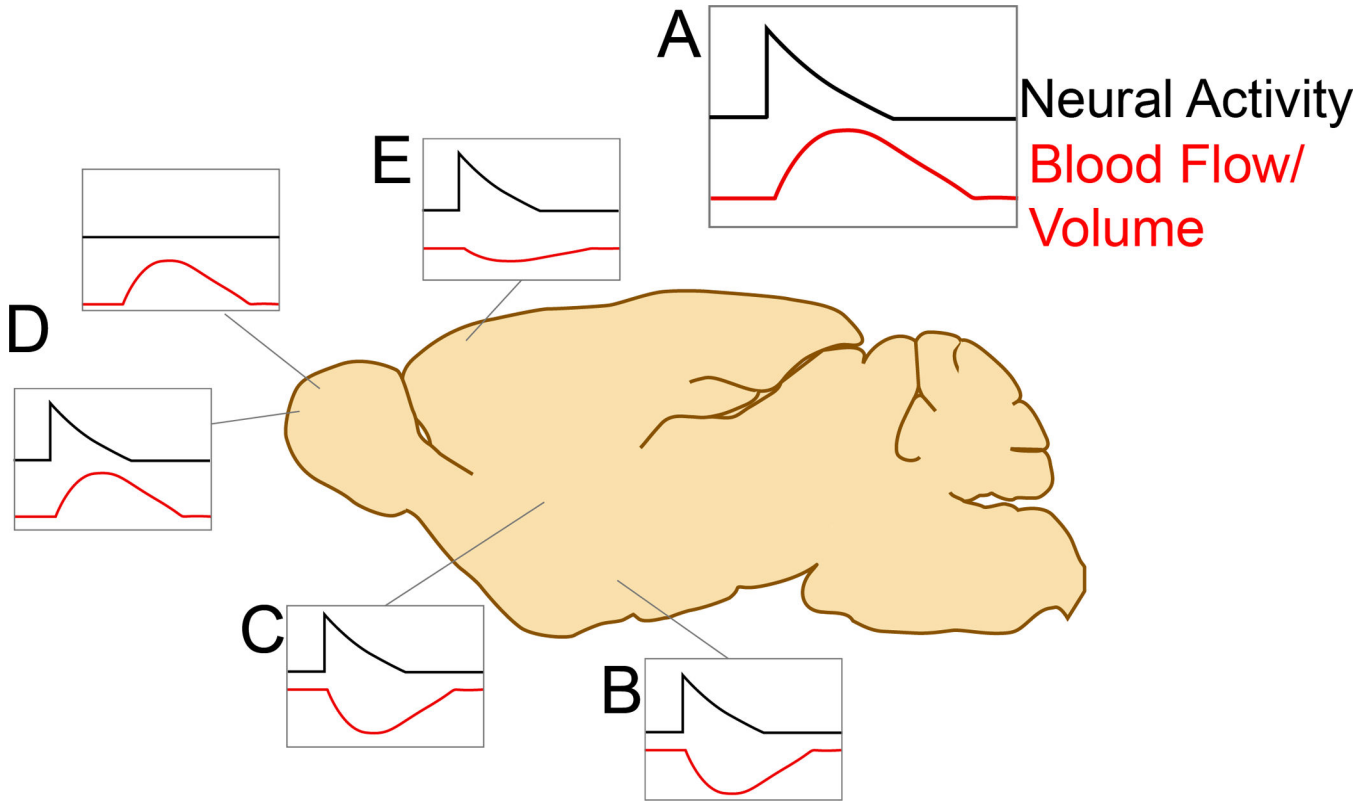

Figure 1.

Examples of non-canonical neurovascular coupling. A) Canonical neurovascular coupling, with a brief increase in neural activity followed by a slower vasodilation and flow increase. B & C) Inversion of neurovascular coupling in hypothalamus [30] and striatum [22]. D) In the olfactory bulb, there are flow increases in areas without neural activity, but nearby activated areas [27]. E) In the frontal cortex, neural activity goes up during locomotion, but there is a slight decrease in blood volume/flow [23–25].

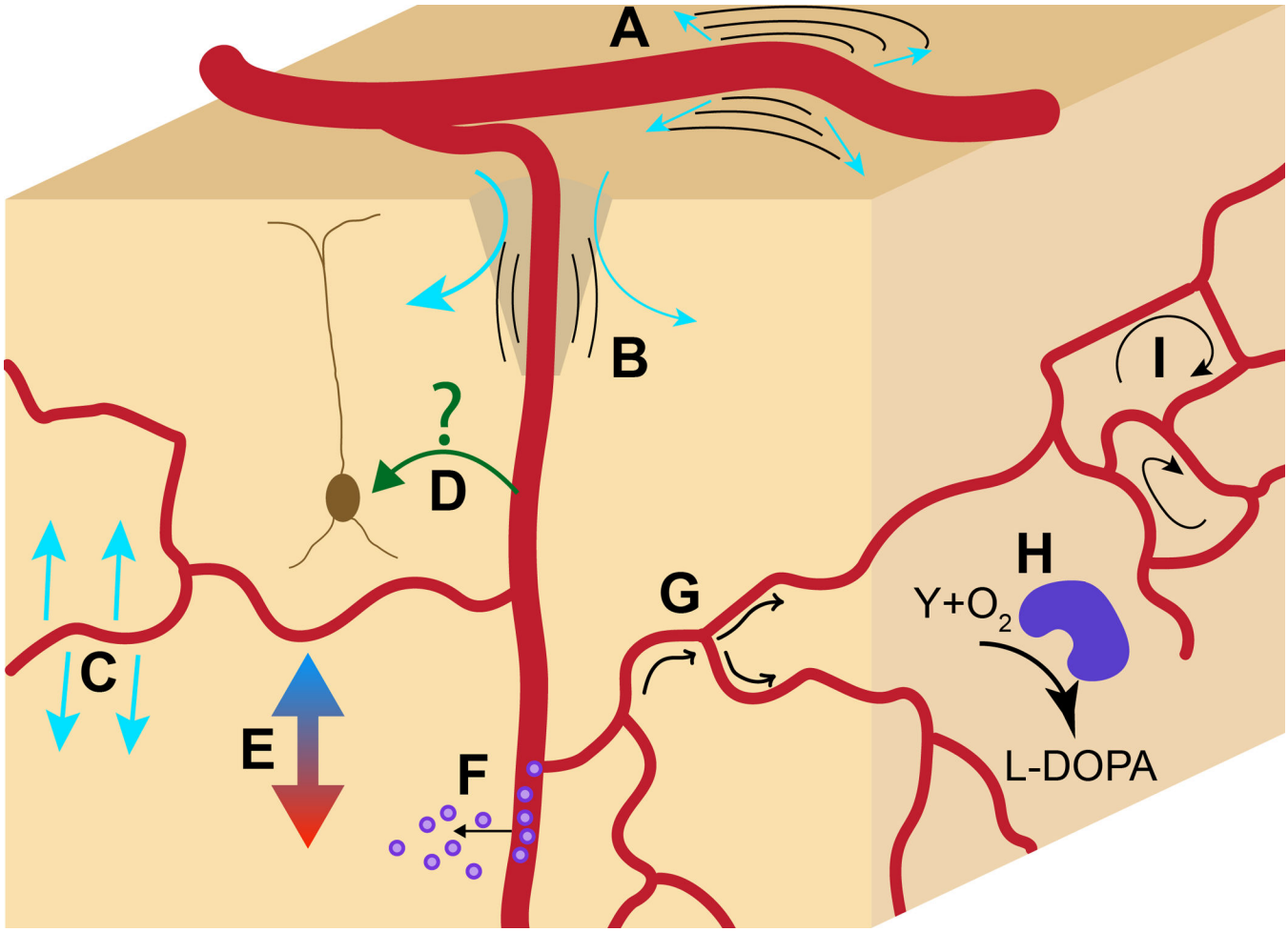

Figure 2.

Potential non-metabolic functions for neurovascular coupling A) Circulation of CSF in the sub-arachnoid space is driven by arterial dilation [97]. B) Arterial dilation can drive convective transport through the brain [100]. C) Elevated pressure drives increased CSF secretion by vasculature [102]. D) Signaling from vasculature to neurons [19,116] E) Maintenance of brain temperature [85]. F) Transmission of signaling molecules from the periphery [65,66]. G) Regularization of non-Newtonian flow [121,122]. H) Providing oxygen for neuromodulator synthesis [54]. I) Mechanical signals for stabilization of vascular topology [131].