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Chapter

Cerebral Vascular Tone Regulation: Integration and Impact of Disease

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Abstract

This chapter summarizes the current knowledge regarding the regulation of the tone of cerebral resistance arteries under conditions of normal health and with the development of chronic diseases (e.g., metabolic disease). The work integrates the myogenic (pressure-induced) regulation of vascular tone, the impact of elevated luminal flow or shear stresses, that of local tissue metabolic activity on vascular tone and the concept of neurovascular coupling (linking neuronal activity to the impacts on vascular diameter). In addition, this work summarizes some of the recent work on how diseases such as type 2 diabetes impact the mechanisms of cerebrovascular tone regulation. It is anticipated that the current review will provide the reader with an up-to-date understanding of how the cerebral resistance vessels respond to changes in their local environment and contribute to the regulation of blood flow within the brain.

Keywords: cerebral, perfusion resistance, metabolic disease, vascular function, vascular disease risk

1. Introduction

The brain has a remarkably high metabolic rate and thus requires a highly disproportional amount of blood flow. Although its only 2% of body weight, the brain takes up 15–20% of cardiac output [1], making it one of the most highly perfused organs in the human body. This high metabolic rate coupled with its limited capacity for energy storage [2] necessitates heavy reliance on oxidative metabolism and thus requires constant blood flow to maintain nutrient and oxygen supply, remove waste products, and maintain a state of cerebral metabolic homeostasis. Severe underperfusion can quickly result in unconsciousness [3] and if prolonged, death [4]; while chronic mild under perfusion is associated with cognitive decline [5]. In addition to its high perfusion and metabolic rate, the cerebral circulation faces a unique challenge of being enclosed in the skull. This rigid structure prevents the expansion of tissue and extracellular fluid. Swelling within the skull from vasogenic edema leads to an increase in intracranial pressure which in turn can lead to neurologic complications or in more extreme cases death [1]. The unique challenges of the cerebral circulation, including intolerance to ischemia and edema, coupled with the paramount importance of maintaining constant nutrient and oxygen supply to cerebral tissue creates a need for precise regulation of cerebral blood flow and therefore the presence of redundant intrinsic mechanisms for its regulation. The anatomy of the brain vasculature ensures multiple routes for blood and oxygen delivery potentially allowing for perfusion even in cases of a blocked blood vessel [6]; however, acute

regulation of flow is done primary by altering the diameter of blood vessels, and thus the resistance to flow. The major mechanisms of local regulation of vascular tone intrinsic to the cerebral vasculature include myogenic, shear, and metabolic based regulation. Although each mechanism has a discrete effect on vascular tone the integration of the different contributors to determine an appropriate level of tone is much more difficult to discern, especially in the cerebral circulation. These complex interactions allow for highly accurate control of cerebral blood flow in addition to protecting vulnerable downstream capillaries from high pressures and flow rates that could otherwise lead to edema; but, they also introduce several potential areas for failure. The intimate interactions of the various mechanisms of regulation of flow mean that the failure of one mechanism has the potential to initiate a cascade of events that results in inappropriate regulation of flow. As such abnormal execution of vascular tone regulation may form the basis of vascular pathologies [7].

One of these pathologies with a significant vascular component associated with impaired cerebral vascular tone regulation is metabolic syndrome (MetS). The incidence and prevalence of MetS is growing in Western society [8–10] and is contributing to decreased quality of life and increased economic burden. Thus an understanding of how it alters the cerebral circulation is crucial. MetS is categorized by a collection of metabolic risk factors including obesity, hypertension, atherogenic dyslipidemia and impaired glycemic control creating a pro-oxidant pro-inflammatory environment that raises the risk of developing impaired vascular structures and function [11–14]. These impairments are particularly detrimental when they affect the cerebral circulation and lead to cerebrovascular pathologies such as stroke or transient ischemic attack (TIA) due to the detrimental consequences associated with such events. However, cognitive impairments are not limited to individuals that have experienced an acute ischemic event since even in their absence MetS is strongly associated with impaired cognitive function and decreased quality of life [15–18]. Therefore preventing their occurrence by protecting the cerebrovasculature from functional and structural decline is paramount. This chapter will present a description of the local mechanisms involved in the regulation of cerebral vascular tone, how they integrate with one another and how they can be compromised in disease. Although impairments to the regulation of cerebral vascular tone are not limited to conditions associated with MetS this discussion will focus on the impact of MetS and its associated risk factors.

2. Myogenic mechanism

The myogenic mechanism which was first described by Bayliss is an intrinsic property of the vascular smooth muscle to respond to changes in intravascular pressure which is independent of other mechanisms of tone regulation including neural, metabolic, and hormonal influences [19]. The intrinsic nature of the myogenic response is supported by its existence in arteries and arterioles that have been sympathetically denervated and had their endothelium removed [20] thus leaving only the vessel itself to initiate and execute the response. The prototypical response of the vascular smooth muscle in response to an increase in intraluminal pressure is initial distension quickly followed by a constriction. The opposite can be said in situations of decreased intraluminal pressure; a fall in intraluminal pressure results in vessel collapse followed by dilation [21]. The myogenic response has several physiological roles including the establishment and maintenance of basal vascular tone (some degree of constriction) so that resistance may be increased or decreased by metabolic vasoconstrictors or vasodilators respectively, in order to regulate tissue perfusion. The establishment and maintenance of this partially constricted state

in a pressurized vessel is referred to as myogenic tone. Additionally, the myogenic tone has a role in flow and pressure regulation. It functions by constricting to drop the pressure that reaches the downstream capillaries and protect them from edema or vascular remodeling associated with hypertension in the capillaries [22–25]. Equally important as protecting from hypertension is the ability of the vasculature to promote flow during low pressure by dilating. This ability to alter diameter over a range of pressures is referred to as myogenic reactivity. Beyond the local implications for the regulation of vascular tone, resistance to flow also has implications for systemic blood pressure since mean arterial pressure is the product of total peripheral resistance and cardiac output. This relationship illustrates system-wide implications of accurate vascular tone regulation. While the myogenic response is present throughout the body in a variety of vessels (arterioles, veins, lymphatic vessels) [26] the aforementioned functions of the myogenic response are particularly important in the cerebral circulation due to the catastrophic outcomes associated with under or over perfusion including unconsciousness and edema respectively. It is therefore not surprising that the most prominent myogenic response is found in the cerebral circulation with arterioles (resistance vessels) having the most pronounced response [1]. It should also be noted that the large arteries feeding the brain have a greater contribution to regulating vascular resistance in the cerebral circulation compared to other vascular beds, again providing evidence for the importance of regulating tone in the cerebral circulation.

A phase model of arterial myogenic behavior is commonly used to describe the response over a range of pressure. In the first phase, there is an initial development of myogenic tone at approximately 40–60 mmHg with increasing pressure up to that point causing passive distension. There is then a phase of myogenic reactivity in the pressure range of 60–140 mmHg and finally a phase of forced dilation at transmural pressures greater than approximately 140 mmHg [27].

2.1 Myogenic tone

Myogenic tone develops at approximately 40–60 mmHg and is characterized by an increase in intracellular Ca^{2+}, of about 200%, followed by a reduction in lumen diameter. This pressure causes cellular deformation, depolarization of the vascular smooth muscle cells (VSMC), and a significant increase in wall tension. Wall tension appears to be the controlled parameter in the myogenic response which is altered during an increase or decrease in transmural pressure. The myogenic response adjusts the diameter of the vessel in an attempt to restore or limit the change in basal wall tension through a negative feedback mechanism [28, 29]. The suggestion that wall tension is the controlled parameter is supported by its correlation with changes in cell calcium and myosin light-chain phosphorylation, a relationship that is not seen with vessel diameter [30, 31].

The mechanism of the myogenic response is attributed to stretch-activated ion channels: including L-type calcium channels, voltage-activated calcium channels and calcium activated potassium channels along with enzymatic mechanisms. Specifically, increased intraluminal pressure causes depolarization of the VSMC membrane and calcium influx by the opening of voltage-gated calcium channels (VGCCs), with the most prominent involvement being from $Ca_{V1.2}$. This influx of Ca^{2+} leads to increased myosin light-chain (MLC) phosphorylation which promotes increased actin/myosin interaction followed by cross-bridge cycling and cell shortening (vasoconstriction) [7, 24, 32–34]. The importance of Ca^{2+} influx in the generation of myogenic tone supported by its complete abolishment under Ca^{2+} free conditions [32, 35]; this is also a technique frequently used to study the passive mechanical characteristics of vessels to determine the degree of vascular

remodeling since the VMSC exhibit a passive response (no force production) its strain is only due to the applied stress applied and the composition of the vessel [36]. Under physiological conditions the magnitude of the constrictor response to increased intraluminal pressure is limited by calcium-activated potassium channels that carry hyperpolarizing current proportional to the intracellular calcium concentration [35]. This negative feedback mechanism is supported by enhanced myogenic constriction being observed following blockade of calcium-activated potassium channel by specific inhibitors of these channels [37–39]. Additionally, at this pressure of 40–60 mmHg there is an activation of enzymatic systems and a complex interaction between matrix metalloproteins, the extracellular matrix, integrins and the cytoskeleton [40–42] that contribute to the myogenic reactivity at higher intraluminal pressures within the range of 60–140 mmHg [27]. This myogenic tone phase can also be characterized as the lower limit of autoregulation, which has important physiological implications. Below this pressure blood flow becomes dependent on blood pressure since the vessel cannot further dilate and begins to collapse as the pressure drops below this point [43]. Having an appropriate lower limit becomes especially important in situations of cerebral ischemia to allow restoration of flow in the presence of hypotension.

2.2 Myogenic reactivity

In this range of intraluminal pressure of 60–140 mmHg where the myogenic tone has already been established increases in pressure generally result in mild constriction and decreased pressure leads to mild dilation. Just as previously discussed for the generation of myogenic tone, increased pressure within this range leads to stretch, depolarization, and constriction of the vascular smooth muscle. However, in the myogenic reactivity phase, there is little change in vessel diameter across the range of pressures along with relatively small increases in Ca^{2+} (<20%) despite sizable increases in force production [27]. Multiple studies suggest an increased sensitivity to Ca^{2+} compared to the previous phase in the development of myogenic tone [20, 27, 44–48]. Increased sensitivity to Ca^{2+} is achieved by inhibition of myosin light chain phosphatase (MLCP) which promotes the accumulation of phosphorylated LC20 without an accompanying increase in calcium-induced myosin light chain kinase activity [49]. The presence of a contractile mechanism that does not require large variation of calcium, such as altering Ca^{2+} sensitivity requires less storage and transmembrane shuttling and is therefore advantageous in terms of conserving Ca^{2+} [35].

There are several proposed mechanisms that regulate Ca^{2+} sensitivity within this phase including, activation of protein kinase C (PKC), RhoA/Rho kinase pathways, and reactive oxygen species (ROS) [27, 35, 44, 46, 50]. The following studies provide evidence for the aforementioned mechanisms of enhanced Ca^{2+} sensitivity in this phase of the myogenic response through the utilization of specific inhibitors or transgenic animal models. Inhibition of PKC stops myogenic vasoconstriction in middle cerebral arteries with no impact on pressure-induced Ca^{2+} elevation [46]. Direct assessment of Ca^{2+} sensitivity by measuring the Ca^{2+}-tone relationship has consistency found decreased sensitivity during Rho kinase inhibition [20, 45]. ROK has also been reported to trigger smooth muscle depolarization during myogenic constriction and limit the extent of depolarization by opening delayed rectifier potassium channels [51, 52]. Arteries from transgenic animals missing NADPH oxidase function show an absence of myogenic activity [53], while mice deficient in superoxide dismutase, an endogenous antioxidant enzyme that catalyzes the breakdown of superoxide radical to H_2O_2, acquired enhanced myogenic reactivity [54]. Additional mechanisms that contribute to the myogenic reactivity phase independent of Ca^{2+} sensitivity include actin cytoskeleton reorganization and thin filament regulation [55, 56].

2.3 Forced dilation

Although the prototypical response of increased intraluminal pressure is a constriction, at excessively high pressures, beyond the autoregulatory range of approximately 140 mmHg, forced dilation often occurs [57]. This process results in a loss of myogenic tone, and thus results in an increase in vessel diameter, rapid increase in wall tension and significant elevation in Ca^{2+} (>50%) [27]. Although the name implies a degree of passiveness in the process, forced dilation is likely an active vasodilation involving K_{Ca} channels, nitric oxide (NO) and or ROS, which are activated to protect the arterial wall from damage [44, 57]. If the pressure is reduced to within the myogenic reactivity range reestablishment of tone and reduction in Ca^{2+} is observed.

3. Response to flow (shear stress)

An increase in flow leads to an increase in a frictional force known as shear that is detected by the endothelial cells lining the vessel lumen as blood moves through a vessel. As such, the magnitude of the shear force is proportional to blood flow. Shear catalyzes physiologically important responses in the cerebral vasculature such as encouraging reperfusion after ischemia, aiding in the hyperemic response to increased metabolic demand, and perhaps protection of downstream capillaries from edema and structural damage. Flow has been found to induce both constrictor and dilator pathways that act on the VSMC and result in a final level of tone taking into account the opposing processes. It is generally accepted that in the peripheral circulation flow leads to dilation; however, in the cerebral circulation the response is more controversial with both constriction and dilation being reported. These opposing observations may be because of a variety of factors including the area of the brain studied, the preparation used or because of interactions with other mechanisms affecting cerebral vascular tone. Within the cerebral circulation, the vertebrobasilar systems appear to elicit flow-mediated dilation, as measured in rats and mice [58] and humans [59]. The increase in flow is sensed by the endothelium, which initiates a negative feedback mechanism in an attempt to decrease the shear stress by dilating. Shear-induced dilation is largely endothelium-dependent and is at least partially mediated by NO [60]. The production of NO is controlled by the enzyme nitric oxide synthase (NOS), particularly endothelial NOS (eNOS), which catalyzes the formation of NO from L-arginine and is itself dependent on phosphorylation by Akt [61, 62]. The NO formed by eNOS then diffuses into the vascular smooth muscle where it activates soluble guanylyl cyclase (sGC) and increases cyclic guanine monophosphate (cGMP) and activating protein kinase G [63, 64]. Activation of protein kinase G opens large-conductance Ca^{2+}-activated K^+ (BKCa) channels reducing intracellular Ca^{2+} which leads to relaxation of the vascular smooth muscle and thus vasodilation [65]. In addition to NO, eNOS can also lead to the formation of H_2O_2 which may also mediate flow-induced dilation [18]. During enzymatic cycling, eNOS produces oxygen radicals [66, 67] which, in the presence of sufficient antioxidants, are converted into H_2O_2 that may then, like NO, activate sGC and lead to dilation [68]. Other endothelium-dependent dilators such as prostaglandins do not appear to be involved in shear-induced dilation since the COX inhibitor indomethacin had no effect on the response to flow [60].

Constriction of cerebral vessels has also been reported in cats [69], rats [70] and human isolated cerebral arteries [71]. Constriction appears to predominate within the carotid circulatory area [58] especially when studies using *ex vivo* isolated vessels. In contrast to the dilator response, flow-induced constriction occurs independent of the endothelium [72, 73]. Although the mechanics for constriction

in response to increased flow is not fully understood it appears to be mediated in part by a combination of integrin signaling, free radicals, and tyrosine kinase. Giving integrin-binding peptides, scavenging ROS by superoxide dismutase (SOD) or inhibiting tyrosine [69] all significantly reduced or eliminated constriction in response to flow. Just as in flow-induced dilation shear stress appears to be the initiating parameter in flow induced constriction whose force can be transduced by integrin signaling [69]. Additionally, Koller and Toth found that flow-induced constriction of cerebral vessels were blocked by inhibiting the synthesis of 20-HETE, thromboxane A_2 receptor, COX activity, and scavenging ROS. From that, they proposed that increase flow activates an AA cascade with metabolism by CYP450 4A enzymes resulting in the production of 20-HETE and ROS which contribute to the constriction via thromboxane A_2/prostaglandin H_2 receptors [71].

The differences in observed responses may also be dependent on whether the study was conducted *in vivo* or *ex vivo*. *Ex vivo* studies typically use a physiologic salt solution that has a much lower viscosity than blood and may be inadequate to stimulate the endothelium to produce endothelium-dependent dilation [74]. Consequently, the *ex vivo* responses to intraluminal shear have been shown to be endothelium-independent [69, 72]. Furthermore, *ex vivo* study generally lack pulsatile flow pumps but those that have been able to employ peristaltic or piston pump have indicated a role for shear-mediated regulation [68, 75, 76]. In contrast, in vivo study has produced more consistent shear-mediated dilation [62, 77]. Raignault et al. showed in a mouse model that the cerebrovascular endothelium optimally integrates shear stress to eNOS-mediated dilation under physiological pulse pressures, a phenomenon that was not seen in static flow conditions [76]. It appears that cerebral arteries are more responsive to a pulsatile environment with a viscose fluid (blood) as is experienced *in vivo* and consequently able to dilate in response to shear stress through endothelium-dependent production of NO [68, 76, 78].

Although flow induced constriction is not usually seen *in vivo* at high flow rates it may play a protective role in the cerebral circulation. Just as low flow situations are dangerous, especially in the brain, so too are instances of extreme flow; therefore it is important to have multiple regulatory mechanisms that are able to attenuate an increase in flow as a protective mechanism for the cerebral circulation from high volumes [1, 79, 80]. It is advantageous for the response to flow to adapt in accordance with other inputs on the regulation of vascular tone. This may be the reason why characterizing the response to flow in the cerebral circulation has been variable. One variable that may alter the response to flow is the absolute rate of flow. In isolated branches of MCA from rats vessels dilated with flow up to 10 μL/min but their diameter constricted back to baseline at higher levels of flow [81]. Shimoda et al. also found a biphasic flow-dependent response in anterior and middle cerebral arteries of neonatal pigs; flow rates between 0.077 and 0.212 mL/min constricted vessels while dilation occurred at higher flow rates up to 1.6 mL/min [82].

3.1 Flow and pressure

In a physiological setting multiple inputs are being processed by the cerebral vasculature leading to the generation of a certain level of tone. Pressure and shear stress exerted by flowing blood are two mechanical stimuli that have been described to play a major role in the regulation of vascular tone [83, 84]. It is therefore important to consider their interaction when determining the resultant effect on vascular tone. At high pressures (around >80 mmHg) cerebral vessels tend to constrict in response to flow [72, 85–87]. This biphasic response is further supported by findings from Garcia-Roldan and Bevan in isolated rabbit pial arterioles with flow rates from 0 to 20 μL/min at 90 mmHg but did not with the same flow at 60 mmHg [72].

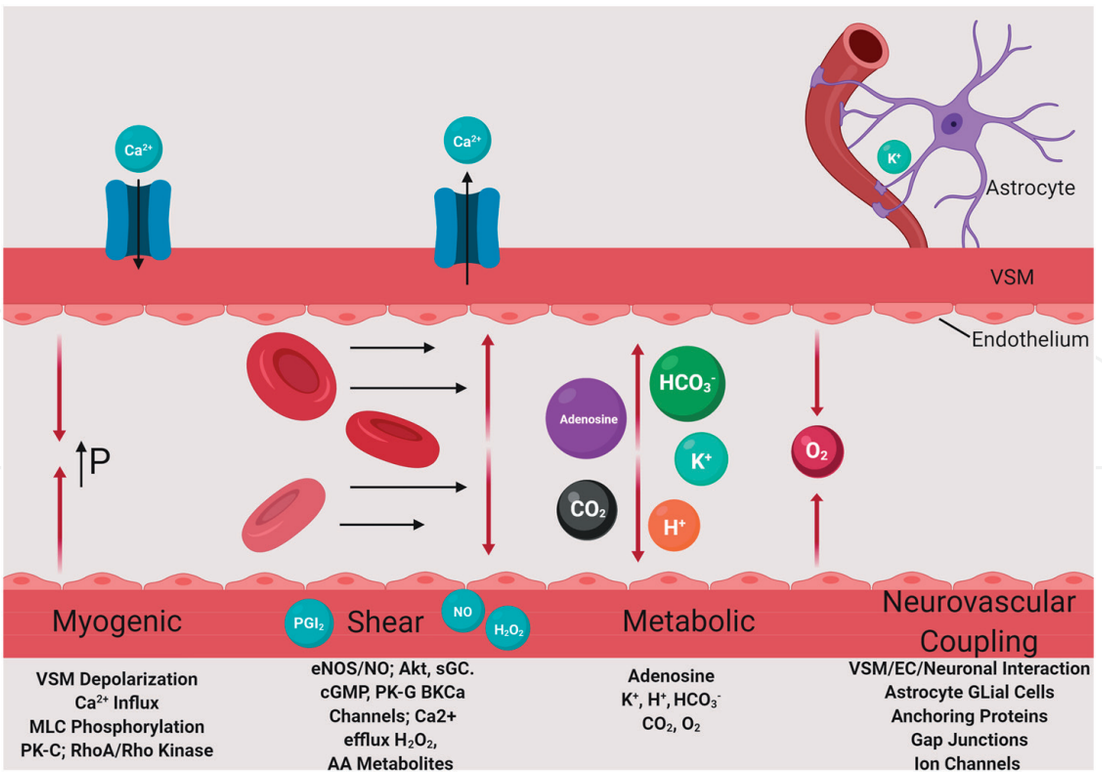

Figure 1.
A schematic representation of how intravascular pressure (myogenic), increased lumen flow rates (shear), tissue metabolism and neurovascular coupling can impact cerebral vascular tone regulation.

It is interesting that the tipping points for "high" and "low" pressures observed in previous studies are around 80 mmHg since, in resistance arterioles such as the MCA this pressure is commonly measured under physiological conditions. If 80 mmHg is indeed the point where higher pressures lead to constriction and lower to dilation in response to shear the resistance arterioles that are resting around this pressure would have the opportunity to tightly regulate the response to flow and shear thus allowing for precise control of cerebral blood flow. Please see **Figure 1** for a schematic representation of how flow and intravascular pressure can impact cerebral vascular tone.

4. Metabolic control

The mechanical stimuli of pressure and flow are generally thought to be important in setting the basal vascular tone so that metabolic influences are able to cause dilation or constriction depending on the needs of the cerebral tissue [24]. Metabolic control of vascular resistance is of particular importance in the cerebral circulation since cerebral tissue is extremely intolerant to ischemia [88]. As such, the cerebral circulation has a precise and highly localized coupling between the metabolic requirements of cerebral tissue and the magnitude of blood flow by controlling vascular resistance. There are numerous vasoactive metabolites that contribute to the control of cerebral vascular tone including adenosine, CO_2, H^+, O_2 and K^+. Increasing concentrations of adenosine, CO_2, H^+, and K^+ and decreased concentration of O_2 result in relaxation of VSM and dilation of cerebral resistance vessels. Each metabolite is associated with a cascade of events that ultimately either alters intracellular Ca^{2+} concentration or Ca^{2+} sensitivity of the VSM and results in a change in vessel diameter. Although the effects of each metabolite have been well characterized the relative importance of each along with its interaction with each other and other parameters of tone remains an area of further investigation. The discussion below is summarized in **Figure 1**.

4.1 Adenosine

Adenosine has been proposed as being the primary metabolite controlling metabolic regulation of cerebral vascular tone. It is a naturally occurring nucleoside produced as a byproduct of ATP metabolism; thus, its accumulation signals a need for increased blood flow to match the metabolic activity. This relationship with metabolism has widely implicated adenosine in local regulation of cerebral vascular tone during functional hyperemia, ischemia, or whenever PO_2 becomes limited [89–91]. Adenosine has direct effects on the vasculature [92, 93] that can both vasodilate and hyperpolarize VSM and is therefore considered an EDHF [94]. There are four distinct subtypes of adenosine receptors; however, the A_{2A} receptor appears to be of high importance in mediating vasodilation [95–97]. The A_{2A} receptor is a purinergic P_1 receptor that has been confirmed to be present in cerebral microvessels [98–101] on the VSM cells [102, 103]. It causes dilation in a concentration-dependent manner [101, 104] once bound to the A_{2A} receptor by activation of adenylate cyclase [105] and therefore cAMP [106–108] which reduces cytosolic calcium and leads to vasodilation. The opening of K_{ATP} channels also occurs secondary to the increase in cAMP levels as a result of adenosine binding to its receptors on the cell membrane [109–112]. The contribution of opening K_{ATP} channels to dilation is likely substantial since during blockade of K_{ATP} channels with glibenclamide, adenosine-induced dilation was reduced by approximately 50% [113]. Although A_{2A} receptors are generally considered the most important mediators of the effects of adenosine on vascular tone the A_{2B} receptors are also proposed to cause dilation through similar mechanisms as A_{2A} in addition to coupling to Gq proteins to produce Ca^{2+} mobilization by activation of phospholipase C and mitogen-activated protein kinase activation [98, 114, 115]. In addition to dilating the cerebral vasculature adenosine may also block vasoconstrictive signals in the parenchyma as evidenced by *in vitro* data from Gordon et al. [116]. When adenosine receptors are blocked with theophylline dilation was attenuated to arterial hypoxia [117]. Similarly the competitive adenosine receptor antagonist aminophylline causes a 20–30% decrease in CBF and cerebral oxygen delivery in normoxia [118].

4.2 PCO_2

Similar to many of the other metabolites discussed CO_2 tends to increase under conditions of increased metabolism without adequate flow to eliminate it from the area of production and thus its accumulation leads to dilation of the vasculature. High sensitivity to PCO_2 is unique to the cerebral circulation [119] causing approximately 3–6% increase and 1–3% decrease in flow per mmHg change in $PaCO_2$ above or below eupnoeic $PaCO_2$ respectively. This high sensitivity is seen throughout the arterial side of the vascular network including the large arteries in the neck [120] and large intracranial arteries [121–123] to the smallest pial arterioles [124] and parenchymal vessels [125–128]. There are likely several redundant mechanistic contributors to the sensitivity of the vasculature to PCO_2 which may contribute to the debate as to whether the dilation is triggered by increased PCO_2 or rather the accompanying increase H^+ concentration from the carbonic anhydrase reaction. There is strong support that the change in PCO_2 mediates at least in part alterations in cerebral vascular tone locally by changes in perivascular pH [107, 129–131] as evidenced by acidic and alkaline perfusate administered through an intracranial window. Experiments that have been able to alter pH and PCO_2 independently have provided evidence of the dependence of altered pH to initiate a change in cerebral vascular tone [74]. In a cat pial arteriole cranial window preparation, lowering pH along with hypercapnia resulted in no difference in the magnitude of vasodilation when compared to acidic isocapnia [132]. Interestingly, vessel tone was unaltered in response to intraluminal CO_2 change,

suggesting that a change in superfusate pH is necessary to evoke a change in cerebral vascular tone [107, 133]. This is supported by the findings of unchanged CBF in humans [107] and animals [133] in response to changes in arterial pH, and highly localized pial arteriolar diameter changes in response to the application of acidic/basic solution into the perivascular space [131]. Additionally, when pH is maintained as seen in an experiment with artificial CSF pretreated with sodium bicarbonate, pial vessel dilation is eliminated in response to intraluminal hypercapnia [107, 134] further supporting that a change in superfusate pH is necessary to alter the cerebral vascular tone. In addition to its link with CO_2 and H^+ through the carbonic anhydrase reaction, there is some evidence that bicarbonate ion may independently influence vascular tone. Having the ability to sense and react to multiple parameters associated with acidosis allows for control of tone in response to not only the pH but also the cause of the disturbance (accumulation of CO_2 for instance). In isolated rat basilar arteries reduced $[HCO_3^-]_o$ has been shown to directly increase cerebral vascular tone (with pH maintained at 7.4 and CO_2 kept constant at 5%) through the binding of receptor protein tyrosine phosphatase through an endothelium-dependent response [135]. HCO_3^- may, therefore, stimulate soluble adenylate cyclase activity through a pH-independent mechanism [136]. If this is correct then the modest increase in $[HCO_3^-]$ during hypercapnia may aid in the dilation response to CO_2 but the opposing vasocontractile response to decreases in $[HCO_3^-]_o$ may limits the vasorelaxation caused by a reduction in pH [135]. Limiting vasorelaxation during acidosis is important to lessen the increase in capillary pressure associated with vasorelaxation of upstream arterioles. Hyper-relaxation may overload the capillaries leading to edema and damage thereby worsening the consequences of local inadequate perfusion.

4.3 PO_2

The effects of oxygen are unique in that its availability is required for aerobic metabolism rather than a byproduct like some of the metabolic factors discussed. Therefore it is not surprising that its abundance leads to vasoconstriction and its relative shortage leads to dilation. Although its availability is tightly linked to that of PCO_2 and H^+ and other metabolic byproducts in a physiological setting, studies have been able to discern its independent effect in the presence of otherwise constant conditions. Data from isolated arteries/arterioles suggest there is in fact an oxygen sensor independent of other vasoactive metabolic byproducts within the vascular wall itself [137–142]. Once the change in oxygen is sensed there are various mediators of hypoxic dilation including endothelial-derived NO [138, 141], prostanoids [137, 140, 141, 143], 20-HETE [141] and EDHF [139]; however, the contribution of each factor appears to be dependent on the severity of hypoxia [141]. In skeletal muscle, dilation from mild hypoxia (15% O_2) was mostly NO-dependent, while moderate (10% O_2) was mediated by a combination of increased PGI_2 and decreased 20-HETE, and severe (0% O_2) was almost entirely accounted for by an increase in PGI_2 [141]. In all cases, there appears to be significant involvement by the endothelium to mediate the dilation, which is further supported by a reduction in hypoxic dilation when isolated vessels were exposed to indomethacin (an inhibitor of AA metabolism and thus the production of PGI_2) [137, 144, 145] and to a lesser degree by L-NAME (an inhibitor of NO production from NOS) [145]. Therefore, PGI_2 is likely a substantial contributor to hypoxic dilation with a lesser but likely still significant role for NO. Human studies measuring CBF with pcMRI, instead of isolated vessel diameter as in the aforementioned studies, with and without administration of L-NAME suggest that hypoxic dilation is highly dependent on NO, with no change from baseline observed in hypoxia when L-NAME was administered [146]. These differences may be because of a species-specific response or differences in *ex vivo* and *in vivo* conditions.

Additional mechanisms of hypoxic dilation include adenosine whose action has previously been discussed. In hyperoxic conditions constriction is favored, mediated by a greater conversion of AA to 20-HETE as opposed to dilators such as PGI_2 [147].

4.4 Potassium and neurovascular coupling

Although K^+ is not directly a byproduct of a metabolite pathway it tends to increase in concentration when the frequency of neuronal depolarization is increased, and is therefore indicative of increased metabolism. K^+ channels are present in cerebrovascular smooth muscle cells and are important regulators of tone because of their ability to alter membrane potential [148, 149]. Although K^+ channels are present through the peripheral vasculature, the cerebral circulation has a unique anatomical feature that allows for intimate interaction of astrocytic endfeet and cerebral vessels. This tight interaction between the astrocytic endfeet and vasculature allows for precise localized changes in blood flow to match the site-specific neural activity in the brain [150, 151]. K^+ can therefore be thought of as a direct link between neuronal activity and blood flow. This pairing of neuronal metabolism with appropriate blood flow and is termed neurovascular coupling (NVC). NVC forms the mechanistic basis for neuroimaging techniques that are able to map changes in neuronal activity based on vascular responses such as changes in blood flow or oxygen saturation [152]. As such, an understanding of NVC is not only crucial to understand the regulation of cerebral vascular tone but is also needed to interpret these neuroimaging techniques including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and near-infrared spectroscopy [153].

NVC is dependent on the interactions of the neurovascular unit which is made up of three major components: the vascular smooth muscle, neuron, and astrocyte glial cell. Somewhat surprisingly, the initiation site of neurovascular coupling is at the level of capillaries which then leads to changes upstream; however, once the close anatomical locations of neurons to the capillaries (8–20 μm) are considered this becomes a logical point of initiation [154]. Not only does NVC rely on interactions apart from the vasculature but it also requires several structural components to facilitate cell-to-cell interactions of these different cell types. These components include gap junctions [155, 156], anchoring proteins [157] and specialized ion channels [158] expressed on cell–cell interface membranes. Neurons initiate NVC by generating direct signals that act on the vasculature and indirect signals that are transmitted through astrocytes and lead to increases in intracellular Ca^{2+} within the astrocyte. This is achieved by the glutamatergic synaptic activity initiating post-synaptic N-methyl-D-receptors (NMDA) and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The increase in intracellular Ca^{2+} activates Ca^{2+}-dependent enzymes to produce vasodilators. Some of the enzymes activated include neuronal NOS (nNOS) and cyclooxygenase 2 (COX-2) [159, 160]. Glutamate also acts on metabotropic glutamate receptors in astrocytes increasing Ca^{2+} in these cells and leading to the production of vasoactive metabolites including adenosine, ATP, and K^+ that act of the VSMCs [161].

Astrocytes are anatomically well positioned to transmit signals from neurons to the vasculature because of their close proximity to the capillaries; however, in a vascular network both the downstream and upstream vasculature must work in concert in order to effectively regulate blood flow delivery. It appears that endothelial cells provide the crucial role of retrograde propagation of the vasomotor response allowing for coordination between up and downstream vasculature. Endothelial cells can produce numerous metabolites including NO, prostanoids, and endothelin to alter VSMCs constriction. Endothelial intermediate K^+ channels (K_{IR}) channels and small conductance K^+ channels (K_{SK}) have been implicated as a

mechanistic contributor to the propagation of the vasodilatory signal upstream for a synchronized hemodynamic response between the capillaries and arterioles via myoendothelial gap junctions [162]. Secondary to the movement of hyperpolarizing current through gap junctions, K^+ efflux from K_{IR} and K_{SK} channels generates what has been described as a "K^+ cloud" [163] that also hyperpolarizes neighboring VSMC through both the inducible Na^+-K^+ electrogenic pump and stimulation of inward rectifying potassium channels in the VSMC of cerebral arteries and arterioles. In both cases, there is a net efflux of K^+ from VSMC [164–167] in conjunction with closed voltage-gated calcium channels and therefore results in the relaxation of the VSMC. The importance of K^+ channels in dilating the cerebral vasculature is supported by reduced K^+ conductance, depolarization and ultimately constriction seen in experimental inhibition of the channels [163]. For example, 6–10 mM K^+ applied to capillaries generated a hyperpolarizing response in endothelial cells which was transmitted upstream to penetrating arterioles hyperpolarizing and relaxing VSMCs [168]. This propagation of the vasodilation signal was blocked with inhibition of K_{IR} with barium or endothelial deletion of $K_{IR1.2}$ channels, supporting its role transmitting the hyperpolarizing current. Interestingly the capillaries themselves did not dilate to K^+ suggesting they act as a sensor detecting the signal for the upstream arterioles to be the effector of the response [161].

Although in a physiological setting K^+ tends to lead to vasodilation, the response to K^+ may be dependent on the $[K^+]$. In isolated cerebral arterioles low (<7 mM) and moderate (8–15 mM) increases in $[K^+]$ result in endothelium-independent dilations and sustained dilation respectively through mechanisms previously discussed [165]. Higher K^+ concentrations cause constriction; however, under normal physiological conditions this concentration is not reached and is only seen under pathological processes such as spreading depression and stroke [169, 170]. This response seen in isolated vessel has also been confirmed in vivo [151]. There is a combination of mechanisms at work in response to K^+ that may explain the opposing responses to different concentrations. Alone an increase in $[K^+]_o$ actually tends to depolarize neighboring VSMC resulting in constriction; this response predominates at high $[K^+]$. At low concentrations, the minor increase in $[K^+]_o$ would by itself lead to constriction but it also stimulates both K_{IR} channels [150, 171–174] and Na^+/K^+ ATPase [175–177] promoting K^+ efflux as previously described. This description of the electrophysiology at work in the VSMC is supported by E_m measurement in VSMCs when a solution containing $[K^+]$ (<20 mM) is applied and produces VSM hyperpolarization, whereas at higher K^+ concentrations depolarization predominates [166, 172, 178]. Ultimately the signals generated by neurons, astrocytes, and endothelial cells must be received and integrated into a final level of tone by the VSMCs. A schematic representation of the impact of neurovascular coupling on cerebral vascular tone is presented in **Figure 1**.

5. Effect of diseased states

Each component implicated in the regulation of tone has a multitude of signals being produce that is intended to affect a vasomotor response from the VSMCs. Signals from myogenic, shear, metabolic, and neurovascular influences may be additive or opposing in their effect on VSMCs and further combine with one another creating intricate and precise regulation of cerebral vascular tone. It is this intricacy however, that also introduces many possible steps in the pathway for an abnormal response to occur. As such changes to the regulation of tone may form the basis of several pathologies including MetS. The contributing risk factors associated with MetS alter the local regulation of cerebral vascular tone by inducing changes in both the structure and function of the vessels. These risk factors include hypertension, T2DM, and obesity

which promote a pro-inflammatory pro-oxidant state. Functionally, MetS is highly linked to increased smooth muscle activation and endothelial dysfunction which has important implications for the ability of a vessel to dilate in response to a multitude of stimuli previously discussed including hypotension, shear, hypoxia, and other metabolic stimuli. Increased myogenic properties are consistently overserved in MetS in multiple vascular beds [179, 180] including in the cerebral circulation [181–183]. This increase in constriction may be due to both a decrease in buffering capacity from endothelial dysfunction and alterations in the vascular smooth muscle itself [183, 184]. Endothelial dysfunction also has implication for shear-induced dilation since it is highly dependent on NO bioavailability which has consistently been shown to be reduced in MetS. The chronic inflammatory state seen in MetS likely contributes to the reduction in NO bioavailability due to increased scavenging to the produced NO by reactive oxygen species since this reduction in NO bioavailability is consistently reported to evolve in parallel with oxidant stress and the development of a chronic inflammatory state [185, 186]. This is supported by improved dilatory reactivity of MCA with the pretreatment of the cell-permeable superoxide dismutase mimetic TEMPOL in a model of T2DM [145]. Interestingly some studies have actually shown an increase in eNOS expression which may be an attempt to compensate for the increased scavenging; however, they too continue to find reduced dilator reactivity [187].

Aside from reduced NO bioavailability, a shift in arachidonic acid metabolism toward constrictors and away from dilators that are highly responsible for hypoxic dilation has been demonstrated [145]. Thus not only does endothelial dysfunction seen in MetS increase cerebrovascular resistance by decreased dilator metabolite production it may also promote the production of constrictors that exacerbate the impaired dilation capacity of cerebral vessels [184, 188]. A change in sensitivity to various metabolites in addition to their differential production may also contribute to differential vasomotor responses. For example, studies using SNP, an exogenous NO donor, while blocking endogenous NO production by eNOS using L-NAME, found smaller relaxation of the MCA in spontaneously hypertensive rats which was attributed to a decreased expression of soluble guanylate cyclase [189–192]. In a model of T2DM decreased sensitivity of MCA to the PGI_2 analog iloprost was also found suggesting that both decrease production and sensitivity of dilators may be contributing to the impaired dilation of the cerebral circulation in MetS [145].

Impaired dilation in response to exogenous dilator metabolites may also be due to vascular remodeling. Structural changes are an important consideration since even if the smooth muscle of a cerebral vessel is able to relax due to metabolic influences resulting in hyperpolarization, remodeling may prevent an increase in lumen diameter which is ultimately the major contributor to acute changes in resistance and thus the regulator of flow. Hypertension is largely implicated in the thickening of the vascular smooth muscle as well as increasing the ratio of collagen to elastin in the vessel. High intraluminal pressure increases the shear stress exerted on the vascular endothelium which normally could be restored to baseline by NO-induced vasodilation [193–195]; however, in a disease state with impaired NO production, there is a reduced ability to dilate resulting in endothelial damage and upregulation of atherogenic genes [193–195]. As a means of protection from chronic increased shear stress and wall tension that may lead to downstream edema cerebral vessels tend to hypertrophy with chronic hypertension, but this protective hypertrophy is also detrimental [188]. Since wall tension is equal to intraluminal pressure X radius and wall stress is wall tension/wall thickness, hypertension-induced hypertrophy and inward remodeling resulting in a decrease in radius and increase wall thickness can normalize both the wall tension and wall stress [188]. Although this remodeling may be protective in regards to increases in pressures and protecting the downstream capillaries from edema it increases the cerebrovascular resistance and limits the dilation reserve during hypotension and therefore presents

itself as a right-shift in the autoregulatory range [196, 197]. The development of myogenic tone at higher pressure implies an increased lower limit of autoregulation. This predisposes cerebral tissue to reduced blood flow during hypotension. When pressure drops below the lower limit flow becomes dependent on the passive diameter of the vessel. Not only does an impaired lower limit predispose hypertensive individuals to ischemia but the reduced passive diameter from vascular remodeling further compromises flow to cerebral tissue resulting in hypoxic areas [43].

In addition to hypertrophy and inward remodeling, there is substantial arterial stiffening commonly seen in MetS. The pro-oxidant stress of ROS may interact with components of the perivascular matrix and initiate collagen cross-linking and deposition as well as the breakdown of elastin making the vessel less distensible [198]. This is measured by a left shift in the stress-strain curve of isolated cerebral vessels under passive conditions achieved by using a Ca^{2+} free solution preventing the development of tone [183]. The stiffening vessel from increased collagen to elastin ratio is made worse by the thickening of vessel walls previously discussed. In a model of T2DM with hypertension significant collagen deposition in addition to medial hypertrophy increasing the wall the lumen ratio and stiffness of the rats MCA [199] was demonstrated while T2DM in the absence of hypertension does not appear to induce structural changes to the cerebral vasculature [145]. This along with data that suggests the increase in arterial stiffness seems to follow a time course similar to that of the onset of hypertension suggests a strong relationship between hypertension and vascular remodeling [200]. Chronic uncontrolled hyperglycemia and inflammation do tend to lead to the development of hypertension and thus contribute to changes in the composition of cerebral vessels and it is likely the combination of both seen in MetS increases the degree to which remodeling occurs. A summary of the impact of disease states on the regulation of cerebral vascular tone is presented in **Figure 2**.

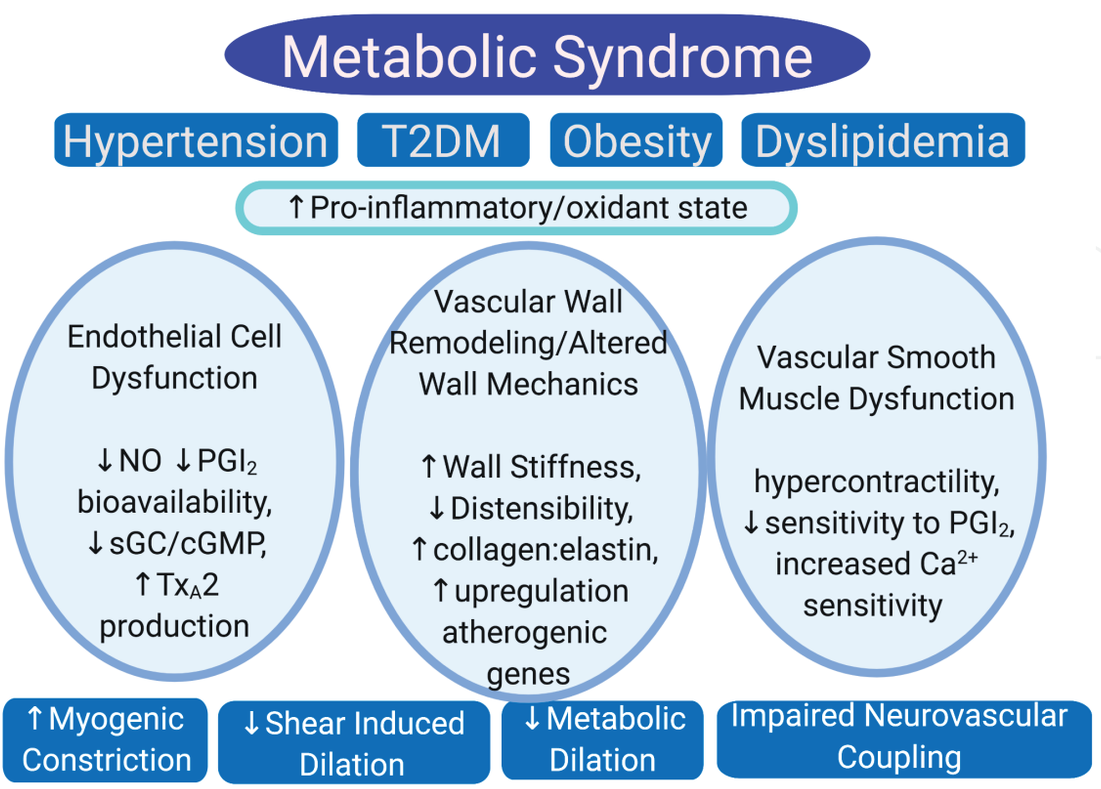

Figure 2.
A schematic representation of how the presence of metabolic syndrome and the major constituent pathologies can impact the integrated regulation of cerebral vascular tone.

6. Conclusions

In conclusion, the regulation of vascular tone involves a complex set of pathways with myogenic, shear, and metabolic control. The mechanical influences of pressure and flow serve as a stimulus for the myogenic and shear responses to set a basal level of tone over a wide range so that metabolic factors have room to produce vasoactive responses on the vasculature. Due to the paramount importance of precise cerebral blood flow control these mechanisms are particularly pronounced and redundant in the cerebral circulation allowing for greater protection against insufficient perfusion or edema and capillary damage in situations of hypotension and hypertension respectively. However, due to the complexity of these homeostatic blood flow mechanisms there is the potential for the development of a pathological state. MetS presents a constellation of cardiovascular risk factors that are highly linked to the development of such cerebrovascular pathologies increasing the risk of stroke, TIA, and vascular dementia. The risk factors associated with MetS result in vascular remodeling which decreases the lumen size and increases stiffness and when paired with endothelial dysfunction and increased activation of the vascular smooth muscle it promotes increased cerebrovascular resistance. This right shifts the autoregulatory zone of myogenic regulation allowing for enhanced protection from hypertension but leaves cerebral tissue vulnerable to underperfusion. Controlling these risk factors and well as implementing targeted therapeutic strategies aimed at ameliorating the regulation of cerebrovascular tone has the potential to restore function in the cerebral circulation and improve current negative outcomes associated with MetS and cerebrovascular dysfunction.

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References

[1] Cipolla MJ. The Cerebral Circulation. San Rafael, CA, USA: Morgan & Claypool Life Sciences; 2010

[2] Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. Glia. 2007;**55**(12):1263-1271

[3] Van Lieshout JJ, Wieling W, Karemaker JM, Secher NH. Syncope, cerebral perfusion, and oxygenation. Journal of Applied Physiology. 2003;**94**:833-848

[4] Smith BA, Clayton EW, Robertson D. Experimental arrest of cerebral blood flow in human subjects: The Red Wing studies revisited. Perspectives in Biology and Medicine. 2011;**54**(2):121-131

[5] Ng TP, Feng L, Nyunt MSZ, Feng L, Gao Q, Lim ML, et al. Metabolic syndrome and the risk of mild cognitive impairment and progression to dementia follow-up of the Singapore longitudinal ageing study cohort. JAMA Neurology. 2016;**73**(4):456-463

[6] Gebremedhin D, Gopalakrishnan S, Harder DR. Endogenous events modulating myogenic regulation of cerebrovascular function. Current Vascular Pharmacology. 2014;**12**(6):810-817

[7] El-Yazbi AF, Abd-Elrahman KS. ROK and arteriolar myogenic tone generation: Molecular evidence in health and disease. Frontiers in Pharmacology. 2017;**8**(87):1-10

[8] Boutayeb A, Boutayeb S, Boutayeb W. Multi-morbidity of non communicable diseases and equity in WHO Eastern Mediterranean countries. International Journal for Equity in Health. 2013;**12**(1):60

[9] De Carvalho VF, Bressan J, Babio N, Salas-Salvadó J. Prevalence of metabolic syndrome in Brazilian adults: A systematic review. BMC Public Health. 2013;**13**:1198

[10] Fu J, Prasad HC. Changing epidemiology of metabolic syndrome and type 2 diabetes in Chinese youth. Current Diabetes Reports. 2014;**14**:447

[11] DeVallance E, Fournier SB, Donley DA, Bonner DE, Lee K, Frisbee JC, et al. Is obesity predictive of cardiovascular dysfunction independent of cardiovascular risk factors? International Journal of Obesity. 2015;**39**:244-253

[12] Donley DA, Fournier SB, Reger BL, DeVallance E, Bonner DE, Olfert IM, et al. Aerobic exercise training reduces arterial stiffness in metabolic syndrome. Journal of Applied Physiology. 2014;**116**(11):1396-1404

[13] Ferdinand KC, Rodriguez F, Nasser SA, Caballero AE, Puckrein GA, Zangeneh F, et al. Cardiorenal metabolic syndrome and cardiometabolic risks in minority populations. Cardiorenal Medicine. 2014;**4**:1-11

[14] Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. Journal of Diabetes Investigation. 2013;**4**(4):334-343

[15] Rosenberg GA. Inflammation and white matter damage in vascular cognitive impairment. Stroke. 2009;**40**(3):S20-S23

[16] Alfaro FJ, Lioutas V-A, Pimentel DA, Chung C-C, Bedoya F, Yoo W-K, et al. Cognitive decline in metabolic syndrome is linked to microstructural white matter abnormalities. Journal of Neurology. 2016;**263**:2505-2514

[17] Tsai C-K, Kao T-W, Lee J-T, Wu C-J, Hueng D-Y, Liang C-S, et al. Increased

risk of cognitive impairment in patients with components of metabolic syndrome. Medicine (Baltimore). 2016;**95**(36):e4791

[18] Yates KF, Sweat V, Yau PL, Turchiano MM, Convit A. Impact of metabolic syndrome on cognition and brain: A selected review of the literature. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012;**32**(9):2060-2067

[19] Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. The Journal of Physiology. 1902;**28**(3):220-231

[20] Schubert R, Kalentchuk VU, Krien U. Rho kinase inhibition partly weakens myogenic reactivity in rat small arteries by changing calcium sensitivity. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**:H2288-H2295

[21] Davis MJ, Sikes PJ. Myogenic responses of isolated arterioles: Test for a rate-sensitive mechanism. American Journal of Physiology. Heart and Circulatory Physiology. 1990;**28** (6 Pt 2):H1890-H1900

[22] Folkow B. Transmural pressure and vascular tone—Some aspects of an old controversy. Archives Internationales de Pharmacodynamie et de Thérapie. 1962;**139**:455-469

[23] Mellander S, Johansson B. Control of resistance, exchange, and capacitance functions in the peripheral circulation. Pharmacological Reviews. 1968;**20**(3):117-196

[24] Davis MJ, Hill MA. Signaling mechanisms underlying the vascular myogenic response. Physiological Reviews. 1999;**79**(2):387-423

[25] Roman R, Dokkum R. Commentary on the special issue on the impact of myogenic tone in health and disease. Current Vascular Pharmacology. 2014;**12**(6):779-780

[26] Von der Weid PY. Lymphatic myogenic constriction—How lymphatic vessels pump lymph uphill. The Journal of Physiology. 2013;**591**(2):391-392

[27] Osol G, Brekke JF, Mcelroy-Yaggy K, Gokina NI. Myogenic tone, reactivity, and forced dilatation: A three-phase model of in vitro arterial myogenic behavior. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**:H2260-H2267

[28] Harder DR. A cellular mechanism for myogenic regulation of cat cerebral arteries. Annals of Biomedical Engineering. 1985;**13**:335-339

[29] Harder DR, Lange AR, Gebremedhin D, Birks EK, Roman RJ. Cytochrome P450 metabolites of arachidonic acid as intracellular signaling molecules in vascular tissue. Journal of Vascular Research. 1997;**34**(3):237-243

[30] Johnson PC. The myogenic response in the microcirculation and its interaction with other control systems. Journal of Hypertension. Supplement. 1989;**7**(4):S33-S40

[31] Zou H, Ratz PH, Hill MA. Role of myosin phosphorylation and $[Ca^{2+}]i$ in myogenic reactivity and arteriolar tone. American Journal of Physiology. Heart and Circulatory Physiology. 1995;**269** (5 pt 2):H1590-H1596

[32] Knot HJ, Nelson MT. Regulation of arterial diameter and wall $[Ca^{2+}]$ in cerebral arteries of rat by membrane potential and intravascular pressure. The Journal of Physiology. 1998;**508**(1):199-209

[33] Moosmang S, Schulla V, Welling A, Feil R, Feil S, Rg JÈ, et al. Dominant role of smooth muscle L-type calcium channel $Ca_{v1.2}$ for blood pressure regulation. European Molecular Biology Organization. 2003;**22**(22):6027-6034

[34] Hill MA, Zou H, Potocnik SJ, Meininger GA, Davis MJ. Invited review: Arteriolar smooth muscle mechanotransduction: Ca^{2+} signaling pathways underlying myogenic reactivity. Journal of Applied Physiology. 2001;**91**(16):973-983

[35] Schubert R, Lidington D, Bolz SS. The emerging role of Ca^{2+} sensitivity regulation in promoting myogenic vasoconstriction. Cardiovascular Research. 2008;**77**(1):8-18

[36] Butcher JT, Goodwill AG, Frisbee JC. The ex vivo isolated skeletal microvessel preparation for investigation of vascular reactivity. Journal of Visualized Experiments. 2012;**62**:e3674

[37] Brayden JE, Nelson MT. Regulation of arterial tone by activation of calcium-dependent potassium channels. Science. 1992;**256**(5056):532-535

[38] Knot H, Standen N, Nelson M. Ryanodine receptors regulate arterial diameter and wall $[Ca^{2+}]$ in cerebral arteries of rat via Ca^{2+}-dependent K^+ channels. The Journal of Physiology. 1998;**508**(1):211-221

[39] Brenner R, Pere ÂZGJ, Bonev AD, Eckman DM, Kosek JC, Wiler SW, et al. Vasoregulation by the B1 subunit of the calcium-activated potassium channel. Nature. 2000;**407**:870-876

[40] D'Angelo G, Mogford JE, Davis GE, Davis MJ, Meininger GA. Integrin-mediated reduction in vascular smooth muscle $[Ca^{2+}]$i induced by RGD-containing peptide. American Journal of Physiology. Heart and Circulatory Physiology. 1997;**272**(4 Pt 2): H2065-H2070

[41] Martinez-Lemus LA, Crow T, Davis MJ, Meininger GA. $\alpha_v\beta_3$- and $\alpha_5\beta_1$-integrin blockade inhibits myogenic constriction of skeletal muscle resistance arterioles. American Journal of Physiology: Heart and Circulatory Physiology. 2005;**289**(1):H322-H329

[42] Lucchesi PA, Sabri A, Belmadani S, Matrougui K. Involvement of metalloproteinases 2/9 in epidermal growth factor receptor transactivation in pressure-induced myogenic tone in mouse mesenteric resistance arteries. Circulation. 2004;**110**:3587-3593

[43] Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. American Journal of Physiology. Heart and Circulatory Physiology. 2013;**304**:H1598-H1614

[44] Paterno R, Heistad DD, Faraci FM. Potassium channels modulate cerebral autoregulation during acute hypertension. American Journal of Physiology: Heart and Circulatory Physiology. 2000;**278**:H2003-H2007

[45] Vanbavel E, Van Der Meulen ET, Spaan JAE. Role of rho-associated protein kinase in tone and calcium sensitivity of cannulated rat mesenteric small arteries. Experimental Physiology. 2001;**86**(5):585-592

[46] Lagaud G, Gaudreault N, Moore EDW, Van Breemen C, Laher I. Pressure-dependent myogenic constriction of cerebral arteries occurs independently of voltage-dependent activation. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**(6):H2187-H2195

[47] Bolz S-S, Vogel L, Sollinger D, Derwand R, Boer C, Pitson SM, et al. Sphingosine kinase modulates microvascular tone and myogenic responses through activation of RhoA/rho kinase. Circulation. 2003;**108**:342-347

[48] Gokina NI, Park KM, Mcelroy-Yaggy K, Osol G. Biomechanics and mechanotransduction in cells and tissues effects of rho kinase inhibition

on cerebral artery myogenic tone and reactivity. Journal of Applied Physiology. 2005;**98**:1940-1948

[49] Somlyo AP, Somlyo AV. Ca^{2+} sensitivity of smooth muscle and nonmuscle myosin II: Modulated by G proteins, kinases, and myosin phosphatase. Physiological Reviews. 2003;**83**:1325-1358

[50] Osol G, Laher I, Cipolla M. Protein kinase C modulates basal myogenic tone in resistance arteries from the cerebral circulation. Circulation Research. 1991;**68**(2):359-367

[51] Yao L, Brayden JE. Rho kinase activity governs arteriolar myogenic depolarization. Journal of Cerebral Blood Flow and Metabolism. 2017;**37**(1):140-152

[52] Luykenaar KD, Abd El-Rahman R, Walsh MP, Welsh DG. Rho-kinase-mediated suppression of KDR current in cerebral arteries requires an intact actin cytoskeleton. American Journal of Physiology. Heart and Circulatory Physiology. 2009;**296**:H917-H926

[53] Nowicki P, Flavahan S, Hassanain H, Mitra S, Holland S, Goldschmidt-Clemont P, et al. Redox signaling of the arteriolar myogenic response. Circulation Research. 2001;**89**:114-116

[54] Veerareddy S, Cooke C-LM, Baker PN, Davidge ST. Gender differences in myogenic tone in superoxide dismutase knockout mouse: Animal model of oxidative stress. American Journal of Physiology. Heart and Circulatory Physiology. 2004;**287**:H40-H45

[55] Cipolla MJ, Osol G. Vascular smooth muscle actin cytoskeleton in cerebral artery forced dilatation. Stroke. 1998;**29**:1223-1228

[56] Morgan KG, Gangopadhyay SS. Invited review: Cross-bridge regulation by thin filament-associated proteins. Journal of Applied Physiology. 2001;**91**:953-962

[57] Jaggar JH, Porter VA, Lederer WJ, Nelson MT. Calcium sparks in smooth muscle. American Journal of Physiology. Cell Physiology. 2000;**278**(2):C235-C256

[58] Koller A, Toth P. Contribution of flow-dependent vasomotor mechanisms to the autoregulation of cerebral blood flow. Journal of Vascular Research. 2012;**49**(5):375-389

[59] Fujii K, Heistad DD, Faraci FM. Flow-mediated dilatation of the basilar artery in vivo. Circulation Research. 1991;**69**(3):697-705

[60] Thorin-Trescases N, Bevan JA. High levels of myogenic tone antagonize the dilator response to flow of small rabbit cerebral arteries. Stroke. 1998;**29**:1194-1201

[61] Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacological Reviews. 1992;**43**(2):109-142

[62] Paravicini TM, Miller AA, Drummond GR, Sobey CG. Flow-induced cerebral vasodilatation in vivo involves activation of phosphatidylinositol-3 kinase, NADPH-oxidase, and nitric oxide synthase. Journal of Cerebral Blood Flow and Metabolism. 2006;**26**(6):836-845

[63] Sobey CG, Faraci FM. Effects of a novel inhibitor of guanylyl cyclase on dilator responses of mouse cerebral arterioles. Stroke. 1997;**28**(4):837-843

[64] Katsuki S, Arnold W, Mittal C, Murad F. Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamine. Journal of Cyclic Nucleotide Research. 1977;**3**(1):23-35

[65] Robertson BE, Schubert R, Hescheler J, Nelson MT. cGMP-dependent protein kinase activates Ca-activated K channels in cerebral artery smooth muscle cells. American Journal of Physiology. Cell Physiology. 1993;**265**(1 pt 1):C299-C303

[66] Porasuphatana S, Tsai P, Rosen GM. The generation of free radicals by nitric oxide synthase. Comparative Biochemistry and Physiology, Part C: Toxicology & Pharmacology. 2003;**134**(3):281-289

[67] Stroes EY, Hijmering M, Zandvoort M, Stroes EY, Hijmering M, Van Zandvoort M, et al. Origin of superoxide production by endothelial nitric oxide synthase. FEBS Letters. 1998;**438**(3):161-164

[68] Drouin A, Thorin E. Flow-induced dilation is mediated by Akt-dependent activation of endothelial nitric oxide synthase-derived hydrogen peroxide in mouse cerebral arteries. Stroke. 2009;**40**:1827-1833

[69] Madden JA, Christman NJT. Integrin signaling, free radicals, and tyrosine kinase mediate flow constriction in isolated cerebral arteries. American Journal of Physiology. 1999;**277**(6):H2264-H2271

[70] Bryan RM, Marrelli SP, Steenberg ML, Schildmeyer LA, Johnson TD. Effects of luminal shear stress on cerebral arteries and arterioles. American Journal of Physiology. Heart and Circulatory Physiology. 2001;**280**:H2011-H2022

[71] Toth P, Rozsa B, Springo Z, Doczi T, Koller A. Isolated human and rat cerebral arteries constrict to increases in flow: Role of 20-HETE and TP receptors. Journal of Cerebral Blood Flow and Metabolism. 2011;**31**:2096-2105

[72] Garcia-Roldan J-L, Bevan JA. Augmentation of endothelium-independent flow constriction in pial arteries at high intravascular pressures. Hypertension. 1991;**17**:870-874

[73] Hoogerwerf N, Zijlstra EJ, van der Linden PJW, Westerhof N, Sipkema P. Endothelium function is protected by albumin and flow-induced constriction is independent of endothelium and tone in isolated rabbit femoral artery. Journal of Vascular Research. 1992;**29**(5):367-375

[74] Hoiland RL, Fisher JA, Ainslie PN. Regulation of the cerebral circulation by arterial carbon dioxide. Comprehensive Physiology. 2019;**9**:1101-1154

[75] Drouin A, Bolduc V, Thorin-Trescases N, Bélanger É, Fernandes P, Baraghis E, et al. Catechin treatment improves cerebrovascular flow-mediated dilation and learning abilities in atherosclerotic mice. American Journal of Physiology. Heart and Circulatory Physiology. 2011;**300**:H1032-H1043

[76] Raignault A, Bolduc V, Lesage F, Thorin E. Pulse pressure-dependent cerebrovascular eNOS regulation in mice. Journal of Cerebral Blood Flow and Metabolism. 2017;**37**(2):413-424

[77] Fujii K, Heistad DD, Faraci FM. Effect of diabetes mellitus on flow-mediated and endothelium-dependent dilatation of the rat basilar artery. Stroke. 1992;**23**(10):1494-1498

[78] Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3′:5′-cyclic monophosphate levels in various tissue preparations. Proceedings of the National Academy of Sciences of the United States of America. 1977;**74**(8):3203-3207

[79] Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. Circulation Research. 1990;**66**:8-17

[80] Faraci FM, Mayhan WG, Heistad DD. Segmental vascular responses to acute hypertension in cerebrum and brain stem. American Journal of Physiology. Heart and Circulatory Physiology. 1987;**252** (4 Pt 2):H738-H742

[81] Ngai AC, Winn HR. Modulation of cerebral arteriolar diameter by intraluminal flow and pressure. Circulation Research. 1995;**77**(4):832-840

[82] Shimoda LA, Norins NA, Jeutter DC, Madden JA. Flow-induced responses in piglet isolated cerebral arteries. Pediatric Research. 1996;**39** (4 Pt 1):574-583

[83] Burnstock G. Neurogenic control of cerebral circulation. Cephalalgia. 1985;**2**:25-33

[84] Jones CJ, Kuo L, Davis MJ, Chilian WM. Myogenic and flow-dependent control mechanisms in the coronary microcirculation. Basic Research in Cardiology. 1993;**88**(1):2-10

[85] Reich T, Rusinek H. Cerebral cortical and white matter reactivity to carbon dioxide. Stroke. 1989;**20**:453-457

[86] de Wit C, Schäfer C, von Bismarck P, Bolz S-S, Pohl U. Elevation of plasma viscosity induces sustained NO-mediated dilation in the hamster cremaster microcirculation in vivo. Pflügers Archiv. European Journal of Physiology. 1997;**434**:354-361

[87] Garcia-Roldan JL, Bevan JA. Flow-induced constriction and dilation of cerebral resistance arteries. Circulation Research. 1990;**66**(5):1445-1448

[88] Peterson EC, Wang Z, Britz G. Regulation of cerebral blood flow. International Journal of Vascular Medicine. 2011;**2011**:8

[89] Berne RM, Richard Winn H, Rubio R. The local regulation of cerebral blood flow. Progress in Cardiovascular Diseases. 1981;**24**(3):243-260

[90] Winn RH, Rubio R, Berne RM. Brain adenosine production in the rat during 60 seconds of ischemia. Circulation Research. 1979;**45**(4):486-492

[91] Bari F, Louis TM, Busija DW. Effects of ischemia on cerebral arteriolar dilation to arterial hypoxia in piglets. Stroke. 1998;**29**:222-228

[92] Ramkumar V, Hallam DM, Nie Z. Adenosine, oxidative stress and cytoprotection. Japanese Journal of Pharmacology. 2001;**86**:265-274

[93] Tabrizchi R, Bedi S. Pharmacology of adenosine receptors in the vasculature. Pharmacology & Therapeutics. 2001;**91**(2):133-147

[94] Ohta M, Toyama K, Gutterman DD, Campbell WB, Lemaître V, Teraoka R, et al. Ecto-5′-nucleotidase, CD73, is an endothelium-derived hyperpolarizing factor synthase. Arteriosclerosis, Thrombosis, and Vascular Biology. 2013;**33**(3):629-636

[95] Wechsler RL, Kleiss LM, Kety SS. The effects of intravenously administered aminophylline on cerebral circulation and metabolism in man. The Journal of Clinical Investigation. 1950;**29**(1):28-30

[96] Gottstein U, Paulson B. The effect of intracarotid aminophylline infusion on the cerebral circulation. Stroke. 1972;**3**:560-565

[97] Magnussen I, Høedt-Rasmussen K. The effect of intraarterial administered aminophylline on cerebral hemodynamics in man. Acta Neurologica Scandinavica. 1977;**55**(2):131-136

[98] Fredholm BB, Ijzerman AP, Jacobson KA, Klotz K-N, Linden J. International Union of Pharmacology.

XXV. Nomenclature and classification of adenosine receptors. Pharmacological Reviews. 2001;**53**(4):527-552

[99] Kalaria RN, Harik SI. Adenosine receptors and the nucleoside transporter in human brain vasculature. Journal of Cerebral Blood Flow and Metabolism. 1988;**8**:32-39

[100] Kalaria RN, Harik SI. Adenosine receptors of cerebral microvessels and choroid plexus. Journal of Cerebral Blood Flow and Metabolism. 1986;**6**:463-470

[101] Phillis JW. Adenosine in the control of the cerebral circulation. Cerebrovascular and Brain Metabolism Reviews. 1989;**1**(1):26-54

[102] Fredholm BB, Abbracchio MP, Burnstock G, Dubyak GR, Harden TK, Jacobson KA, et al. Towards a revised nomenclature for P1 and P2 receptors. Trends in Pharmacological Sciences. 1997;**18**(3):79-82

[103] Brunton L, Chabner B, Knollman B. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. New York City, NY, USA; 2011

[104] Ngai AC, Winn HR. Effects of adenosine and its analogues on isolated intracerebral arterioles extraluminal and intraluminal application. Circulation Research. 1993;**73**:448-457

[105] Anand-Srivastava MB, Franks DJ, Cantin M, Genest J. Presence of "Ra" and "P"-site receptors for adenosine coupled to adenylate cyclase in cultured vascular smooth muscle cells. Biochemical and Biophysical Research Communications. 1982;**108**(1):213-219

[106] de Jong J, de Jonge R, Keijzer E, Bradamante S. The role of adenosine in preconditioning. Pharmacology & Therapeutics. 2000;**87**(2-3):141-149

[107] Kontos HA, Wei EP, Jarrell Raper A, Patterson JL. Local mechanism of CO_2 action on cat pial arterioles. Stroke. 1977;**8**(2):226-229

[108] Li Y-O, Fredholm BB. Adenosine analogues stimulate cyclic AMP formation in rabbit cerebral microvessels via adenosine A2-receptors. Acta Physiologica Scandinavica. 1985;**124**:253-259

[109] Bryan PT, Marshall JM. Adenosine receptor subtypes and vasodilatation in rat skeletal muscle during systemic hypoxia: A role for A1 receptors. The Journal of Physiology. 1999;**514**(1):151-162

[110] Danialou G, Vicaut E, Sambe A, Aubier M, Boczkowski J. Predominant role of A1 adenosine receptors in mediating adenosine induced vasodilatation of rat diaphragmatic arterioles: Involvement of nitric oxide and the ATP-dependent K^+ channels. British Journal of Pharmacology. 1997;**121**:1355-1363

[111] Kuo L, Chancellor JD. Adenosine potentiates flow-induced dilation of coronary arterioles by activating K_{ATP} channels in endothelium. American Journal of Physiology. 1995;**269** (2 pt 2):H541-H549

[112] Li Q, Puro DG. Adenosine activates ATP-sensitive K^+ currents in pericytes of rat retinal microvessels: Role of A1 and A2a receptors. Brain Research. 2001;**907**(1-2):93-99

[113] Carter RW, Kanagy NL. Tyrosine kinases regulate intracellular calcium during 2-adrenergic contraction in rat aorta. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**:H1673-H1680

[114] Klinger M, Freissmuth M, Nanoff C. Adenosine receptors: G protein-mediated signalling and the role of accessory proteins. Cellular Signalling. 2002;**14**(2):99-108

[115] Linden J. Molecular approach to adenosine receptors: Receptor-mediated mechanisms of tissue protection. Annual Review of Pharmacology and Toxicology. 2001;**41**:775-787

[116] Gordon GRJ, Choi HB, Ellis-Davies GCR, Macvicar BA. Brain metabolic state dictates the polarity of astrocyte control over the cerebrovasculature. Nature. 2008;**456**(7223):745-749

[117] Morii S, Ngai AC, Ko KR, Winn HR. Role of adenosine in regulation of cerebral blood flow: Effects of theophylline during normoxia and hypoxia. American Journal of Physiology. Heart and Circulatory Physiology. 1987;**253**(1 pt 2):H165-H175

[118] Willie CK, Tzeng Y-C, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. The Journal of Physiology. 2014;**592**(5):841-859

[119] Ainslie PN, Ashmead JC, Ide K, Morgan BJ, Poulin MJ. Differential responses to CO_2 and sympathetic stimulation in the cerebral and femoral circulations in humans. The Journal of Physiology. 2005;**566**(2):613-624

[120] Willie CK, Macleod DB, Shaw AD, Smith KJ, Tzeng YC, Eves ND, et al. Regional brain blood flow in man during acute changes in arterial blood gases. The Journal of Physiology. 2012;**590**(12):3261-3275

[121] Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. Neurosurgery. 1993;**32**(5):737-742

[122] Wilson MH, Edsell ME, Davagnanam I, Hirani SP, Martin DS, Levett DZ, et al. Cerebral artery dilatation maintains cerebral oxygenation at extreme altitude and in acute hypoxia—An ultrasound and MRI study. Journal of Cerebral Blood Flow and Metabolism. 2011;**31**:2019-2029

[123] Willie CK, Smith KJ, Day TA, Ray LA, Lewis NCS, Bakker A, et al. Regional cerebral blood flow in humans at high altitude: Gradual ascent and 2 wk at 5,050 m. Journal of Applied Physiology. 2014;**116**:905-910

[124] Wolff HG. Cerebral circulation. Archives of Neurology and Psychiatry. 1930;**23**(6):1097

[125] Binks AP, Cunningham VJ, Adams L, Banzett RB. Gray matter blood flow change is unevenly distributed during moderate isocapnic hypoxia in humans. Journal of Applied Physiology. 2008;**104**:212-217

[126] Mandell DM, Han JS, Poublanc J, Crawley AP, Kassner A, Fisher JA, et al. Selective reduction of blood flow to white matter during hypercapnia corresponds with leukoaraiosis. Stroke. 2008;**39**:1993-1998

[127] Nöth U, Kotajima F, Delchmann R, Turner R, Corfield DR. Mapping of the cerebral vascular response to hypoxia and hypercapnia using quantitative perfusion MRI at 3T. NMR in Biomedicine. 2008;**21**(3):464-472

[128] Piechnik SK, Chiarelli PA, Jezzard P. Modelling vascular reactivity to investigate the basis of the relationship between cerebral blood volume and flow under CO_2 manipulation. NeuroImage. 2008;**39**:107-118

[129] Betz E, Enzenrob HG, Vlahov V. Interaction of H^+ and Ca^{++} in the regulation of local pial vascular resistance. Pflfigers Archive. 1973;**343**:79-88

[130] Liu X, Li C, Falck JR, Harder DR, Koehler RC. Relative contribution of cyclooxygenases, epoxyeicosatrienoic acids, and pH to the cerebral blood

flow response to vibrissal stimulation. American Journal of Physiology. Heart and Circulatory Physiology. 2012;**302**:H1075-H1085

[131] Wahl M, Deetjen P, Thurau K, Ingvar DH, Lassen NA. Micropuncture evaluation of the importance of perivascular pH for the arteriolar diameter on the brain surface. Pflügers Archiv. 1970;**316**:152-163

[132] Kontos HA, Raper AJ, Patterson JL. Analysis of vasoactivity of local pH, PCO_2 and bicarbonate on pial vessels. Stroke. 1977;**8**(3):358-360

[133] Harper AM, Bell RA. The effect of metabolic acidosis and alkalosis on the blood flow through the cerebral cortex. Journal of Neurology, Neurosurgery, and Psychiatry. 1963;**26**(4):341-344

[134] Koehler RC, Traystman RJ. Bicarbonate ion modulation of cerebral blood flow during hypoxia and hypercapnia. American Journal of Physiology. 1982;**243**(1):H33-H40

[135] Boedtkjer E, Hansen KB, Boedtkjer DMB, Aalkjaer C, Boron WF. Extracellular HCO_3^- is sensed by mouse cerebral arteries: Regulation of tone by receptor protein tyrosine phosphatase y. Journal of Cerebral Blood Flow and Metabolism. 2015;**36**(5):965-980

[136] Chen Y, Cann MJ, Litvin TN, Iourgenko V, Sinclair ML, Levin LR, et al. Soluble adenylyl cyclase as an evolutionarily conserved bicarbonate sensor. Science. 2000;**289**(5479):625-628

[137] Busse R, Förstermann U, Matsuda H, Pohp U. The role of prostaglandins in the endothelium-mediated vasodilatory response to hypoxia. Pflügers Archiv. 1984;**401**:77-83

[138] Lynch FM, Austin C, Heagerty AM, Izzard AS. Adenosine and hypoxic dilation of rat coronary small arteries: Roles of the ATP-sensitive potassium channel, endothelium and nitric oxide. American Journal of Physiology. Heart and Circulatory Physiology. 2006;**290**:H1145-H1150

[139] Liu Q, Flavahan NA. Hypoxic dilatation of porcine small coronary arteries: Role of endothelium and K_{ATP} channels. British Journal of Pharmacology. 1997;**120**:728-734

[140] Messina EJ, Sun D, Koller A, Wolin MS, Kaley G. Role of endothelium-derived prostaglandins in hypoxia-elicited arteriolar dilation in rat skeletal muscle. Circulation Research. 1992;**71**:790-796

[141] Frisbee JC, Maier KG, Falck JR, Roman RJ, Lombard JH. Integration of hypoxic dilation signaling pathways for skeletal muscle resistance arteries. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2002;**283**:R309-R319

[142] Myers PR, Banitt PF, Guerra R, Harrison DG. Role of the endothelium in modulation of the acetylcholine vasoconstrictor response in porcine coronary microvessels. Cardiovascular Research. 1991;**25**:129-137

[143] Myers PR, Muller JM, Tanner MA. Effects of oxygen tension on endothelium dependent responses in canine coronary microvessels. Cardiovascular Research. 1991;**25**:885-894

[144] Busse R, Pohl U, Kellner C, Klemm U. Endothelial cells are involved in the vasodilatory response to hypoxia. Pflügers Archiv. 1983;**397**:78-80

[145] Halvorson BD, Whitehead SN, Mcguire JJ, Wiseman RW, Frisbee JC. Endothelium-dependent impairments to cerebral vascular reactivity with type 2 diabetes mellitus in the Goto-Kakizaki

rat. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2019;**317**:R149-R159

[146] Van Mil AHM, Spilt A, Van Buchem MA, Bollen ELEM, Teppema L, Westendorp RGJ, et al. Nitric oxide mediates hypoxia-induced cerebral vasodilation in humans. Journal of Applied Physiology. 2002;**92**:962-966

[147] MacVicar BA, Newman EA. Astrocyte regulation of blood flow in the brain. Cold Spring Harbor Perspectives in Biology. 2015;**7**:1-15

[148] Faraci FM, Sobey CG. Role of potassium channels in regulation of cerebral vascular tone. Journal of Cerebral Blood Flow and Metabolism. 1998;**18**:1047-1063

[149] Rosenblum WI. ATP-sensitive potassium channels in the cerebral circulation. Stroke. 2003;**34**:1547-1552

[150] Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson K, Aldrich RW, et al. Local potassium signaling couples neuronal activity to vasodilation in the brain. Nature Neuroscience. 2006;**9**(11):1397-1403

[151] Villringer A, Dirnagl U. Coupling of brain activity and cerebral blood flow: Basis of functional neuroimaging. Cerebrovascular and Brain Metabolism Reviews. 1995;**7**(3):240-276

[152] Lecrux C, Hamel E. The neurovascular unit in brain function and disease. Acta Physiologica. 2011;**203**(1):47-59

[153] Hyder F. Dynamic imaging of brain function. Methods in Molecular Biology. 2009;**489**:3-21

[154] Schlageter KE, Molnar P, Lapin GD, Groothuis DR. Microvessel organization and structure in experimental brain tumors: Microvessel populations with distinctive structural and functional properties. Microvascular Research. 1999;**58**(3):312-328

[155] Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M. Signaling at the gliovascular interface. The Journal of Neuroscience. 2003;**23**(27):9254-9262

[156] Figueroa XF, Duling BR. Gap junctions in the control of vascular function. Antioxidants & Redox Signaling. 2009;**11**(2):251-266

[157] Del Zoppo GJ, Milner R. Integrin-matrix interactions in the cerebral microvasculature. Arteriosclerosis, Thrombosis, and Vascular Biology. 2006;**26**(9):1966-1975

[158] Brayden JE, Earley S, Nelson MT, Reading S. Transient receptor potential (TRP) channels, vascular tone and autoregulation of cerebral blood flow. Clinical and Experimental Pharmacology & Physiology. 2008;**35**:1116-1120

[159] Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T. What is a pericyte? Journal of Cerebral Blood Flow and Metabolism. 2016;**36**(2):451-455

[160] Lecrux C, Hamel E. Neuronal networks and mediators of cortical neurovascular coupling responses in normal and altered brain states. Philosophical Transactions of the Royal Society B: Biological Sciences. 2016;**371**(1705):1-13

[161] Iadecola C. The neurovascular unit coming of age: A journey through neurovascular coupling in health and disease. Neuron. 2017;**96**(1):17-42

[162] Sokoya EM, Burns AR, Setiawan CT, Coleman HA, Parkington HC, Tare M. Evidence for the involvement of myoendothelial gap junctions in EDHF-mediated relaxation in the rat middle cerebral

artery. American Journal of Physiology. Heart and Circulatory Physiology. 2006;**291**:H385-H393

[163] Hannah RM, Dunn KM, Bonev AD, Nelson MT. Endothelial SK_{Ca} and IK_{Ca} channels regulate brain parenchymal arteriolar diameter and cortical cerebral blood flow. Journal of Cerebral Blood Flow and Metabolism. 2011;**31**(5):1175-1186

[164] Nguyen T, Richard Winn H, Janigro D. ATP-sensitive potassium channels may participate in the coupling of neuronal activity and cerebrovascular tone. American Journal of Physiology. Heart and Circulatory Physiology. 2000;**278**:H878-H885

[165] McCarron JG, Halpern W. Potassium dilates rat cerebral arteries by two independent mechanisms. American Journal of Physiology. 1990;**259**(3 Pt 2):H902-H908

[166] Knot HJ, Zimmermann PA, Nelson MT. Extracellular K^+-induced hyperpolarizations and dilatations of rat coronary and cerebral arteries involve inward rectifier K^+ channels. The Journal of Physiology. 1996;**492**(2):419-430

[167] Zaritsky JJ, Eckman DM, Wellman GC, Nelson MT, Schwarz TL. Targeted disruption of Kir2.1 and Kir2.2 genes reveals the essential role of the inwardly rectifying K current in K-mediated vasodilation. Circulation Research. 2000;**87**:160-166

[168] Longden TA, Dabertrand F, Koide M, Gonzales AL, Tykocki NR, Brayden JE, et al. Capillary K^+-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. Nature Neuroscience. 2017;**20**(5):717-726

[169] Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiological Reviews. 2001;**81**(3):1065-1096

[170] Vyskočil F, Kríž N, Bureš J. Potassium-selective microelectrodes used for measuring the extracellular brain potassium during spreading depression and anoxic depolarization in rats. Brain Research. 1972;**39**:255-259

[171] Haddy FJ, Vanhoutte PM, Feletou M. Role of potassium in regulating blood flow and blood pressure. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2006;**290**:R546-R552

[172] Edwards FR, Hirst GDS, Silverberg GD. Inward rectification in rat cerebral arterioles; involvement of potassium ions in autoregulation. The Journal of Physiology. 1988;**404**:455-466

[173] Quayle JM, Mccarron JG, Brayden JE, Nelson MT. Inward rectifier K^+ currents in smooth muscle cells from rat resistance-sized cerebral arteries. American Journal of Physiology. 1993;**265**(5 pt 1):C1363-C1370

[174] Robertson BE, Bonev AD, Nelson MT. Inward rectifier K^+ currents in smooth muscle cells from rat coronary arteries: Block by Mg^{2+}, Ca^{2+}, and Ba^{2+}. American Journal of Physiology. 1996;**271**(2 pt 2): H696-H705

[175] Bünger R, Francis JH, Querengässer A, Gerlach E. Studies on potassium induced coronary dilation in the isolated guinea pig heart. Pflügers Archiv. 1976;**363**:27-31

[176] Haddy F. Potassium effects on contraction in arterial smooth muscle mediated by Na^+, K^+-ATPase. Federation Proceedings. 1983;**42**(2):239-245

[177] Hermsmeyer K. Sodium pump hyperpolarization-relaxation in rat

caudal artery. Federation Proceedings. 1987;**42**(2):246-252

[178] Burns WR, Cohen KD, Jackson WF. K^+-induced dilation of hamster cremasteric arterioles involves both the Na^+/K^+-ATPase and inward-rectifier K^+ channels. Microcirculation. 2004;**11**:279-293

[179] Frisbee JC, Maier KG, Stepp DW. Oxidant stress-induced increase in myogenic activation of skeletal muscle resistance arteries in obese Zucker rats. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**:H2160-H2168

[180] Hayashi K, Kanda T, Homma K, Tokuyama H, Okubo K, Takamatsu I, et al. Altered renal microvascular response in Zucker obese rats. Metabolism. 2002;**51**(12):1553-1561

[181] Jarajapu YPR, Guberski DL, Grant MB, Knot HJ. Myogenic tone and reactivity of cerebral arteries in type II diabetic BBZDR/Wor rat. European Journal of Pharmacology. 2008;**579**:298-307

[182] Phillips SA, Sylvester FA, Frisbee JC. Oxidant stress and constrictor reactivity impair cerebral artery dilation in obese Zucker rats. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2005;**288**:R522-R530

[183] Brooks SD, DeVallance E, D'Audiffret AC, Frisbee SJ, Tabone LE, Shrader CD, et al. Metabolic syndrome impairs reactivity and wall mechanics of cerebral resistance arteries in obese Zucker rats. American Journal of Physiology. Heart and Circulatory Physiology. 2015;**309**(11):H1846-H1859

[184] Baumbach GL, Faraci FM, Heistad DD. Effects of local reduction in pressure on endothelium-dependent responses of cerebral arterioles. Stroke. 1994;**25**:1456-1462

[185] Barbato JE, Zuckerbraun BS, Overhaus M, Raman KG, Tzeng E. Nitric oxide modulates vascular inflammation and intimal hyperplasia in insulin resistance and the metabolic syndrome. American Journal of Physiology. Heart and Circulatory Physiology. 2005;**289**:H228-H236

[186] Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation. 2005;**111**:1448-1454

[187] Kazuyama E, Saito M, Kinoshita Y, Satoh I, Dimitriadis F, Satoh K. Endothelial dysfunction in the early- and late-stage type-2 diabetic Goto-Kakizaki rat aorta. Molecular and Cellular Biochemistry. 2009;**332**:95-102

[188] Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. Journal of Cerebral Blood Flow and Metabolism. 2018;**38**(12):2129-2149

[189] González JM, Beatriz S, Conde MV, Fernández-Alfonso MS, González MC, Arribas SM. Hypertension increases middle cerebral artery resting tone in spontaneously hypertensive rats: Role of tonic vasoactive factor availability. Clinical Science. 2008;**114**:651-659

[190] Bauersachs J, Bouloumié A, Mülsch A, Wiemer G, Fleming I, Busse R. Vasodilator dysfunction in aged spontaneously hypertensive rats: Changes in NO synthase III and soluble guanylyl cyclase expression, and in superoxide anion production. Cardiovascular Research. 1998;**37**:772-779

[191] López-Farré A, Rodriguez-Feo JA, García-Colis E, Gomez J, López-Blaya A, Fortes J, et al. Reduction of

the soluble cyclic GMP vasorelaxing system in the vascular wall of stroke-prone spontaneously hypertensive rats: Effect of the α1-receptor blocker doxazosin. Journal of Hypertension. 2002;**20**(3):463-470

[192] Ruetten H, Zabel U, Linz W, Schmidt HHHW. Downregulation of soluble guanylyl cyclase in young and aging spontaneously hypertensive rats. Circulation Research. 1999;**85**(6):534-541

[193] Humphrey JD. Mechanisms of arterial remodeling in hypertension coupled roles of wall shear and intramural stress. Hypertension. 2008;**52**(2):195-200

[194] Davies PF, Polacek DC, Handen JS, Helmke BP, DePaola N. A spatial approach to transcriptional profiling: Mechanotransduction and the focal origin of atherosclerosis. Trends in Biotechnology. 1999;**17**(9):347-351

[195] Davies PF. Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. Nature Clinical Practice. Cardiovascular Medicine. 2009;**6**(1):16-26

[196] Heistad DD, Baumbach GL. Cerebral vascular changes during chronic hypertension: Good guys and bad guys. Journal of Hypertension. Supplement. 1992;**10**(7):S71-S75

[197] Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. Cell Metabolism. 2008;**7**(6):476-484

[198] Chantler PD, Frisbee JC. Arterial function in cardio-metabolic diseases: From the microcirculation to the large conduits. Progress in Cardiovascular Diseases. 2015;**57**:489-496

[199] Harris AK, Hutchinson JR, Sachidanandam K, Johnson MH, Dorrance AM, Stepp DW, et al. Type 2 diabetes causes remodeling of cerebrovasculature via differential regulation of matrix metalloproteinases and collagen synthesis role of endothelin-1. Diabetes. 2005;**54**:2638-2644

[200] Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension: Emerging concepts. Hypertension. 2010;**55**(1):9-14