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CONTRIBUTION OF FLOW-DEPENDENT VASOMOTOR MECHANISM TO THE AUTOREGULATION OF CEREBRAL BLOOD FLOW

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Abstract

Regulation of cerebral blood flow (CBF) is the result of multilevel mechanisms to maintain blood supply for the brain, in the same time it has to comply with the limited space available in the cranium. This latter requirement is ensured by the autoregulation of CBF, in which the pressure-sensitive myogenic response is known to play a pivotal role. However, in vivo increases in pressure are accompanied by increases in flow; the effects of flow on the vasomotor tone of cerebral vessels are less known. Earlier studies, showing flow-sensitive dilation and/or constriction or both, thus no clear picture emerged. Recently an important role of flow sensitive mechanism(s) eliciting constriction of cerebral vessels has been demonstrated, thus this review focuses on the effect of hemodynamic forces (especially intraluminal flow) on the vasomotor tone of cerebral vessels and the underlying cellular and molecular mechanisms. A novel concept of autoregulation of CBF is proposed suggesting that (in certain areas of the cerebrovascular tree) pressure- and flow-induced constrictions together maintain an effective autoregulation, and alterations of these mechanisms may contribute to the development of cerebrovascular disorders. Future studies are warranted to explore the signals, details of signaling processes and in vivo importance of these mechanisms.

Keywords

flow-induced response; myogenic response; 20-HETE; ROS; cerebral circulation

Introduction

Regulation of cerebral blood flow (CBF) is of utmost importance to supply the myriad function of the brain. It has to ensure many roles: appropriate supply of nutrition and gas for cerebral tissue, fluid and gas exchange in the capillaries, maintenance of cerebral blood volume, thus intracranial volume and pressure in a very limited range. Obviously, such a complex function requires complex regulatory mechanisms ensured by the dynamic interaction of mechanotransduction, metabolic (for example adenosine), chemical (such as changes in pCO2, pH and pO2) and other factors, for example, recently there are emerging evidence regarding an important role for glial (astrocytes), pericytes and neural control of CBF [1–14].

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Because all of these mechanisms have to comply with limited space in the closed cranium [15], maintenance of a relatively constant cerebral blood flow despite of the variations in pressure and flow historically has been always in the center of investigation. Although, autoregulation of CBF is used to be explained by the pressure sensitive myogenic mechanism (here we do not include metabolic and other factors in the notion of autoregulation, we define autoregulation as the sum of the mechanisms activated in response to changes in blood pressure) [4–7, 16–19], careful analysis of earlier data and recent findings question the sole role of myogenic mechanism eliciting autoregulation of CBF [20–24].

Thus, in this review we focus on the potential flow-dependent autoregulatory mechanisms and provide an explanation of the different results of previous studies regarding flow-induced diameter changes of cerebral vessels.

I. Autoregulation of CBF

1) General considerations

Total cerebral blood flow has to be relatively constant in order to allow a stable and continuous supply of cerebral tissue and maintain intracranial volume and pressure constant. On the basis of Hagen-Poiseuille law it can be assumed that CBF is related to the 4^{th} power of vessel radius, thus an increase in the diameter of vessels elicits an *exponential* increase in blood flow. Therefore in the closed cranium, a general vasodilatation would lead to substantial increase in CBF and cerebral blood volume (CBV) and would lead to elevation of intracranial pressure (and vice versa) [19, 25]. Thus, tight control of CBF and CBV is essential for the organism. Indeed, in a wide range (from ~ 60 to 140 mmHg) of perfusion pressure CBF increases only slightly in a *linear* manner measured by different in vivo techniques [5, 18]. At this point it has to be noted, that however in mathematical models gain = 1 is used to indicate so called perfect autoregulation [22, 23], as also depicted in Figure 2, it is likely that such perfect horizontal relationship does not exist in vivo and it would not be beneficial regarding appropriate supply of brain tissue with blood, either. Rather, as Rosenblum suggested it is likely that the slope increases linearly as pressure and flow increases [5, 18, 26, 27]. The linear and not exponential (!) increase of CBF in the face of increasing blood pressure is achieved by the mechanisms of cerebral autoregulation. In this review we do not include metabolic factors into the term of autoregulation, however by some authors metabolic factors/mechanisms are also considered to contribute to “autoregulation” of CBF. This interpretation of “autoregulation” means adjusting CBF to the metabolic demands and to function of neural tissues. Although metabolic regulation of CBF [2, 5, 13, 14, 28] is obviously an important issue, in this review we define autoregulation to be vasomotor responses to changes in hemodynamic forces achieved by mechanisms intrinsic to the vascular wall, rendering the cerebral blood perfusion independent from changes in systemic blood pressure, and without activating metabolic, chemical, glial, neural and other (for example capillary blood flow regulation by pericytes) regulatory mechanisms [1, 2, 5–11, 18, 19, 29]. Because changes in pressure are accompanied by changes in flow, in vivo responses of cerebral vessels to changes in hemodynamics are most likely a combination of pressure and flow-induced mechanisms [30–33]. Thus one can hypothesize that changes in flow contributes to autoregulation of CBF. In other words, in vivo when systemic pressure changes diameter responses of cerebral vessels thus changes of CBF are determined by the combined effect of pressure and flow.

2) Regional and segmental differences in autoregulation of CBF

Autoregulation of cerebral blood flow was documented in a variety of animal species and human using in vivo techniques, such as clearance of diffusible indicators, observation of

pial vessels, measurements of arterial inflow and venous outflow, autoradiography, distribution of radioactive microspheres, and recently by various magnetic resonance imaging, ultrasound and other techniques [18, 34–42].

Importantly, in the cerebral circulation large arteries represent a significant part (≈40 %) of total cerebrovascular resistance [9, 18, 43–45]. In the late 1970's, Kontos at al. investigating the cat pial circulation found that large surface vessels from the circle of Willis to pial arterioles up to 200 micrometer contribute ≈30% of cerebrovascular resistance at 120 mmHg intraluminal pressure and proposed that these vessels are exclusively responsible for autoregulation between 120 and 160 mmHg intraluminal pressure [18]. Similar findings were observed in the rat cerebral circulation [44]. These results showing that in the cerebral circulation both large arteries and small arterioles take part in regulation of CBF indicated that there might have been a hierarchy in vascular responsiveness, a basis for more complicated regulation. This also raised the possibility of spatial characteristics of cerebral autoregulation. Indeed, regional differences were shown in cerebral autoregulatory capacity: hypertension exceeded autoregulation in the cerebrum of the cat (supplied by the internal carotid system), but not in brain stem (supplied by the vertebro-basilar system) demonstrating that autoregulation of flow is more effective in the vasculature of the brain stem [41, 46, 47]. In human cerebral circulation regional differences have also been shown regarding autoregulatory function [48, 49].

However, different magnitude of response in cerebral arteries and arterioles to elevation in pressure was already shown by Kontos et al. [18], later it was proposed again then proved by Faraci and Heistad at al. that different segmental responses of cerebral vessels to changes in intraluminal pressure underlies the heterogeneity of autoregulation. They demonstrated that pial arteriolar pressure is greater in brain stem than in the cerebrum implying that pressure drop is greater on larger arteries in the cerebrum than in the brain stem. Also they found that resistance of larger arteries increase in the cerebrum and decrease in the brain stem during moderate increase in blood pressure. They concluded that autoregulation depended on arterioles in the brain stem, but in the cerebrum larger vessels play an important role in autoregulation [50, 51]. These findings are in line with the findings of Kontos at al. that in the cerebrum larger arteries play a significant part in autoregulation.

3) Physiological role

Collectively, autoregulation ensures that CBF remains relatively constant in a wide range despite increase or decrease of systemic blood pressure. In vivo, autoregulation of CBF shows regional and segmental differences. In the brain stem (supplied by the vertebro-basilar system) resistance of larger arteries decreases whereas that of arterioles increases in response to elevation in pressure. In contrast, in the cerebrum (supplied by the internal carotid artery system) larger arteries increase their resistance to elevation in pressure greater than the arterioles, playing primary role in autoregulation, and protecting downstream brain circulation from pressure and volume overload [43, 50, 52].

It is important to note however, that in these in vivo studies of autoregulation of CBF and cerebrovascular response to pressure the effects of pressure and flow could not be separated and the effect of flow on the diameter of vessels was not even considered [18, 34, 36–43, 50, 53].

II. Pressure-induced myogenic responses of cerebral vessels

1) Earlier findings and conclusions

Until very recently, cerebral autoregulation (relative independence of CBF from changes in systemic blood pressure, especially at higher pressure values) is primarily explained by the

pressure-induced myogenic response [52]: the inherent property of vascular smooth muscle to dilate to decrease and to constrict to increase in intraluminal pressure. Since its first description by Bayliss [35], early in the 20th century the myogenic response of different arteries has been widely investigated. In the cerebral circulation it was first showed by Fog, Forbes and Wolff that pial arterioles of the cat actively dilate and constrict to changes of blood pressure [8, 54, 55]. These findings were confirmed later in studies mentioned above investigating the regulation of CBF, measuring also the simultaneous changes of blood flow, arteriolar pressure etc.

First in the 1980's and since that time, presence of myogenic response has been also shown in vitro in isolated cerebral arteries [22, 56]. In these in vitro studies investigating the myogenic response only pressure was changed, flow was kept constant (this could be done due to the development of novel technics in which by cannulation of vessel on both ends the intraluminal pressure could be raised by increasing both the inflow and outflow pressure or by closing the outflow end of the vessel and increasing the inflow pressure. In both cases the intraluminal flow remains unchanged) [57–59]. Therefore the observed diameter responses were due to changes in pressure alone and were not influenced by changes in flow. Interestingly, in many of these studies cerebral vessels only maintained a constant diameter between 60–140 mmHg intraluminal pressure [20–22, 24]. This response is referred as the 2nd phase of in vitro arterial myogenic behavior proposed by Osol at al [21]. If however, one extrapolated this finding to in vivo conditions, because of the constant diameter, increasing pressure would result in an increasing blood flow velocity thus increasing CBF. In contrast, in vivo measurements of CBF did show that CBF remained relatively constant while intraluminal pressure (and flow velocity) increased! These observations should have prompted the investigators to hypothesize the existence of a flow sensitive mechanism, as well, resulting in further constriction.

However, in many vascular beds the myogenic constriction alone likely prevents increases in blood flow during increases in pressure, for example in the cremaster muscle circulation [60]. Although, the direct comparison of cerebral vessels to peripheral vessels has to be carried out carefully, for instance, Bohlen and Harper [61] and Meininger et al. [62] found that magnitude of myogenic constriction in arterioles of the cremaster muscle is greater than in the comparable sized arterioles of the rat cerebral cortex.

Also, the strength of the myogenic constriction or dilation can be modulated by other effects. For example, hypertension and exercise can enhance the myogenic response leading to increased constriction to increase in intraluminal pressure [22, 61, 63, 64]. Also, myogenic dilation can increase significantly under certain conditions. For instance, arterioles in the cat sartorius muscle dilate significantly more to decrease in intraluminal pressure during sympathetic nerve stimulation, enhancing myogenic dilation and providing increasing flow [65]. Although, in case of increasing blood pressure in cerebral vessels the myogenic constriction is considered to be the most important mechanisms maintaining constant or near constant blood flow [52, 63, 66]. In contrast, as we mentioned above, in most cerebral vessels the myogenic response does not reduce the diameter of vessels beyond the basal level in response to elevation of intraluminal pressure [20–24]. It cannot be excluded however, that magnitude of the myogenic constriction have regional and size differences, and that these vessels possess strong and efficient myogenic response. At present however the investigation of myogenic response of microvessels deeply seeded in the brain is technically challenging and the presence of confounding mechanisms in vivo makes it difficult to interpret the findings. The ratio of the magnitude of pressure (and flow-induced, see later) responses in different brain regions and their contribution to cerebral autoregulation should be clarified in the future.

2) Molecular mechanisms of the myogenic response of cerebral vessels

Although there are several excellent reviews [67–71] of molecular mechanisms of myogenic response, we felt that it would be still appropriate to give a brief overview here.

It is now widely accepted that the primary stimulus to trigger the myogenic response is the pressure-elicited stretch of vascular wall, leading to increased wall tension [72]. However, the sensors are still in question: among others stretch-activated cation channels, Gq-coupled receptors, and interactions between matrix metalloproteinases, extracellular matrix, integrins and the cytoskeleton were proposed [73–76].

The first event in the mechanotransduction is the depolarization of smooth muscle membrane [77]. Although, there is no consensus regarding the initiators of membrane depolarization, stretch-activated cation channels (TRPC6, TRPM4), calcium-activated potassium channels and chloride channels are probably involved [78–83]. Activation of voltage-gated potassium channels limits depolarization as a negative-feedback mechanism [84].

Depolarization of the membrane then leads to the opening of voltage-gated Ca^{2+} channels (which are also capable to respond to stretch directly [85]) and thus elevated inward Ca^{2+} current [86, 87]. Ca^{2+} can be released from sarcoplasmic stores, as well; however their role in myogenic response seems to be minor [85, 88]. The increased Ca^{2+} concentration via Ca^{2+}-calmodulin complex leads to myosin light-chain kinase (MLCK) activation. MLCK phosphorylates myosin light chain (MLC_{20}) leading to increased actin-myosin interaction and consequent shortening of smooth muscle cell [89–91]. Because of the circumferential orientation of the smooth muscle cells shortening is translated into constriction of the vessel.

Interestingly, after the initial elevation the intracellular Ca^{2+} concentration does not increase, but the vessel is still constricting [21]. Among others this observation resulted in the discovery of novel Ca^{2+}-independent mechanisms of the myogenic response which can sensitize the constrictor apparatus to Ca^{2+}. As it was mentioned an increased actin-myosin interaction and consequent shortening of smooth muscle cell depends on the phosphorylated state of MLC_{20}, which is governed by myosin light-chain kinase (MLCK) and myosin light-chain phosphatase (MLCP) [71, 92]. Ca^{2+}-independent mechanisms altering Ca^{2+} sensitivity of smooth muscle cell act through regulation of MLCP. PKC activation, production of diacylglycerol, RhoA/Rho kinase are involved in these processes [71, 92–94].

As a second messenger, 20-hydroxyeixosatetraenoic acid (20-HETE) was also found to play a role in myogenic response (also in other vascular beds) [3, 95–97]. 20-HETE is capable to inhibit large conductance Ca^{2+}-activated K+ channels and to increase influx of Ca^{2+} via L-type Ca^{2+} channels [3, 96, 98]. Also, one of the major molecular targets of 20-HETE is PKC [3, 96, 98, 99].

Collectively, there are two critical mechanisms (Ca^{2+}-dependent and independent) contributing to myogenic constriction: 1) increase in pressure via increase in wall tension and smooth muscle cell stretch leads to membrane depolarization, Ca^{2+} influx and constriction via MLCK and phosphorylation of MLC_{20}. 2) In the same time, Ca^{2+}-independent mechanisms involving PKC, diacylglycerol, RhoA/Rho kinase and 20-HETE regulate the activity of MLCP determining the phosphorylated state of MLC_{20} thus sensitizing actin-myosin to Ca^{2+}.

III. Flow-induced responses of cerebral vessels

As we have mentioned above, changes in pressure are accompanied by changes in flow [30–33], and based on theoretical considerations flow-induced mechanisms may play a role in

cerebral autoregulation. Interestingly, flow-induced responses of cerebral vessels varied between species, vessel types and methods used. In theory, flow-induced dilation would reduce the magnitude of myogenic constriction of cerebral vessels, which would reduce the gain of autoregulation of CBF, whereas if flow elicited constriction, it could contribute to a more efficient autoregulation of CBF. In the following we summarize the results of studies regarding flow-induced responses of cerebral vessels.

1) Diameter responses of isolated cerebral vessels differ to increases in flow

a) Dilation of cerebral vessels to flow—First Fujii at al. showed that basilar artery of rat dilated *in vivo* when intraluminal flow was increased [100, 101]. They used craniotomy to visualize basilar artery. Metabolic parameters (blood O_2 and CO_2, pH) were maintained at a constant physiological level, and blood pressure was kept constant by controlled bleeding of the animal. Intraluminal flow was elevated in the basilar artery by bilateral carotid artery occlusion. It is of note, that among in vivo methods this approach is able to separate the effect of flow and pressure on vessel diameter, while other factors (i.e. metabolic) are controlled. However it cannot be entirely excluded that occlusion of the carotid arteries, which decreases blood flow in the carotid system would generate a signal propagating to basilar artery to elicit dilation. The group of Sobey confirmed dilation of basilar artery using the same method [102]. In 1993, Gaw and Bevan found also dilation of rabbit cerebral vessels using a wire myograph [103], in which however flow and pressure cannot be controlled properly. Recently, Drouin at al. demonstrated flow-induced dilation in cerebral arteries. They studied isolated posterior and anterior cerebral arteries of mice in a pressure-flow chamber in a well-controlled manner [104, 105]. In recent in vitro studies (unpublished observation) we confirmed that in isolated rat basilar arteries increases in flow elicit dilation. An original record of such response is depicted on Figure 1, showing substantial dilation of an isolated basilar artery of rat to increases in flow.

b) Biphasic response of cerebral vessels to flow—Interestingly, there have been studies, in which biphasic response, dilation and constriction of cerebral vessels to increases in flow was observed. Garcia Roldan and Bevan showed that isolated rabbit pial arteries dilated to 20 μl/min flow at 30 mmHg and they constricted to the same flow at 90 mmHg of intraluminal pressure [106, 107]. They used a Halpern perfusion system, in which at a constant pressure, flow was generated by pressure difference due to changing the perfusion by the inflow and outflow pumps.

Thorin-Trescases at al. confirmed these findings also in rabbit cerebral vessels. They found in secondary and tertiary branches of posterior cerebral arteries that flow induced dilation at 40 mmHg, dilation and a small constriction at 60 mmHg, and a small dilation followed by constriction at 80 mmHg intraluminal pressures [108]. Ward at al. observed similar pressure dependency of flow-induced response of cerebral vessels: in arteriolar branches (≈ 80 μm) of the rat posterior cerebral artery flow elicited dilation at 60 mmHg, and constriction at 120 mmHg intraluminal pressure [109].

Ngai and Winn studied arteriolar branches of rat middle cerebral arteries (MCA), approximately 35–88 μm in diameter. They achieved increasing flow at a constant (60 mmHg) pressure by changing the inflow and outflow pressure to an equal degree, but opposite direction (the same method used by us when constrictions were observed in rat MCA and human intracerebral arteries to increases in flow). They also observed that isolated cerebral arterioles, branches of MCA dilated to flow up to 10 μl/min, then restored their diameter at higher flow rates to the initial value [110].

Similar flow-rate dependency was found by Shimoda at al. Anterior and middle cerebral arteries of the neonatal pig constricted to flow between 0.077–0.212 ml/min, and dilated

when flow was raised further (up to 1.6 ml/min). There were no differences in the flow-induced responses at 20 and 60 mmHg intraluminal pressures. In these studies flow was initiated by a syringe pump, and pressure was measured in both the inflow and outflow cannulas by transducers. When flow was raised a micromanipulator decreased the outflow pressure adjacent to the increase in pressure due to flow by sensing the pressure difference between the transducers. The luminal pressure was also measured by inserting a cannula into the lumen of the vessel [111].

In a study Garcia Roldan and Bevan found the mixture of pressure and flow-rate dependency of flow-induced response of cerebral vessels. In isolated rabbit pial arterioles they demonstrated that vessels constricted in response to increase in intraluminal flow from 0 to 20 μl/min at 90 mmHg, but did not at the presence of 60 mmHg of intraluminal pressure. Increasing flow up to 100 μl/min constricted vessels at both pressure values [107]. It has to be clear, that biphasic response of diameter to flow does not mean that vessels exhibit opposite responses in a temporal manner, instead it reflects different responses at different pressure values or flow rates.

c) Constriction of cerebral vessels to increases flow—The variation of observed diameter responses of cerebral vessels in response to increases in flow prompted further investigations. Madden at al. studied isolated cat middle cerebral arteries. They applied 1–4 ml/min flow at 70 and 100 mmHg intraluminal pressures, and found that increases in flow led to decrease in diameter and depolarization of smooth muscle cell membrane. Arteries constricted by flow dilated when PCO_2 was increased, implying that metabolic/chemical signals can override flow-induced constriction. Also, when flow was stopped vessels dilated, and when flow was suddenly increased to the maximal values constriction occurred. Endothelium denudation did not affect flow response, suggesting that flow-induced constriction is endothelium-independent [112].

Sipkema at al. found flow-induced constriction in isolated basilar artery of the Rhesus monkey and in order to make sure that the conditions did not influence the response in the same set up they used isolated femoral arteries as well in which they observed dilation to flow. However, in many of these earlier studies changes in pressure during changes in flow could not be excluded with great certainty. Therefore constriction in these studies to flow could be elicited by the activation of myogenic mechanism, whereas dilation of femoral artery to flow might be caused by flow-induced mechanism, and/or passive dilation (femoral arteries did not develop spontaneous tone). This conclusion is supported by the finding that the active pressure-diameter curves of these vessels did not differ from the passive diameter obtained in calcium free conditions [113]. However, to our best knowledge this is the only study investigating isolated cerebral arteries of monkeys, thus it cannot be excluded that constriction of the basilar artery to flow may be due to species characteristic.

In 2001 Bryan at al. aimed to clarify the controversial findings (dilation, constriction and biphasic responses) regarding flow-induced responses of cerebral vessels. They proposed that controversy and confusion in previous studies were due to different species, different vessel types, different techniques and technical problems causing artifacts, namely the different pH of the extraluminal and intraluminal bath (cerebral vessels are highly sensitive to pH), and the pressure-change accompanying the increase in flow. Therefore in the same experimental conditions they investigated isolated middle cerebral arteries (MCA), penetrating cerebral arterioles (PA) (≈ 70 μm) and cremaster muscle arterioles (CMA) (which are known to dilate to flow) of rats. They used a syringe pump to generate flow, and decreased the outflow pressure according to the elevation in pressure due to flow both counted by an algorithm based on the resistance of the tubing and micropipettes and by measuring directly the intraluminal pressure. They made sure that the flow was laminar

adjusting the necessary length of the vessel. Maximal flow for PA was 40 μl/min, for MCA 300–500 μl/min. They allowed to equilibrate the perfusate before entering the vessel lumen passing it through gas permeable tubing in the extraluminal bath in order to avoid pH differences. In this experimental setup CMA dilated, MCA and PA constricted to increases in flow. The diameter decreased as a function of calculated shear stress, as well (discussed later) [114].

Recently, we have also investigated isolated middle cerebral arteries of the rat [23]. The sizes of glass pipettes used in this study were matched to both each other and the diameter of the vessels in order to achieve equal resistance. In addition, inflow and outflow reservoirs and position of the chamber were built in a symmetrical manner providing equal pressures or generating flow in the presence of constant pressure in the midsection of vessels. We raised pressure, then flow, then pressure and flow together and measured the diameter changes. We found that rat middle cerebral arteries constricted to increases in flow (also see at Figure 1), and flow-induced constriction enhanced the only pressure-induced constriction. Importantly, in line with findings of Bryan at al. [114] flow-induced constriction was observed in smaller vessels, as well. We have found that not only large arteries (i.e middle cerebral arteries) but smaller side branches of MCA (about 50 micrometer in diameter) also constricted to increases in flow (unpublished observation). Also, very recently Filosa's group demonstrated flow-induced constriction of rat cerebral arterioles in brain slices [115].

It is important to note that isolated middle cerebral arteries maintain a stable steady state diameter in the presence of a constant flow rate. Upon increase in flow they constrict and in response to decrease in flow they dilate and maintain the new diameter [23]. These findings suggest that in vitro steady state flow rates activate vasomotor mechanisms that are able to provide a stable diameter. It is likely however that in vivo if such diameter is not sufficient to maintain adequate CBF other mechanisms are activated to provide the sufficient flow to brain tissues. For example, metabolic dilator adenosine inhibited functionally the flow-induced constriction, proposing that metabolic factors can override the flow-induced responses (similar to the case of increase in CO_2, as shown by Madden at al.; see earlier in this section) [23].

Human cerebral arteries constrict to flow, as well: Importantly, we also found that isolated human intracerebral arteries (from the internal carotid circulatory area) constricted to increases in flow, and the flow-induced constriction was mediated by 20-HETE (See later the mechanisms of flow-induced responses) [23]. It has to be noted that the active internal diameters of these vessels were approximately 200–250 μm, equal with the studied rat middle cerebral arteries. These size of vessels correspond to large arteries of the circle of Willis in the rat, but small arteries in the human brain. Also, the human vessels were isolated from the fronto-temporal cortex of patients, thus different responses of human cerebral vessels to flow from different brain regions cannot be excluded.

In conclusion, studies using a well-controlled methodological approach found dilation to flow in rat and mice in the vertebro-basilar circulatory area; constriction was found in cat, rat and importantly, in human isolated cerebral arteries from the internal carotid circulatory area; biphasic responses were observed in rabbit and rat cerebral arterioles showing pressure and flow-rate dependency (dilated at lower and constricted at higher pressure and flow-rates).

2) What are the potential signals of flow-induced responses of cerebral vessels?

Changes in flow are accompanied by changes of many factors, among others wall shear stress. It is widely established that in most vascular beds changes of flow are sensed by the endothelium by sensing wall shear stress (WSS) elicited by increases in flow. The

consequent flow-induced dilation reduces WSS, thus WSS is regulated in a negative feedback manner [57–59]. This can be described by the following equation:

$$WSS=4\eta \times Q/\pi \times r^3,$$

where WWS is wall shear stress, η is viscosity, Q is flow and r is vessel radius [59]. It is believed that the overall physiological ”purpose” of this mechanism is to optimize the circulatory energy loss. This mechanism is likely to play role in the development of functional hyperemia, for example during exercise (in skeletal and cardiac muscle) [57]. In case of cerebral vessels, in which flow elicits dilations - for example in the basilar artery – such WSS-sensitive mechanism can be at operation.

It is more difficult to envision the *mechanotransduction of flow-induced constriction*. What could be the signal that associated with increasing flow and sensed and converted to mechanical responses? Many previous studies were very careful to exclude any changes in intraluminal pressure during the investigation and observation of flow-induced constriction by keeping pressure constant [112, 114], thus increase in pressure cannot be the possible trigger.

The easiest hypothesis would be that in some cerebral vessels increasing WSS is converted to constriction instead of dilation by an unknown mechanism. For example, 20-HETE, the mediator of flow-induced constriction in MCA can cause dilation in basilar arteries known to dilate to flow, because it is converted into - as of yet unknown - dilator metabolites [116]. In this case constriction can be the function of WSS as calculated by Bryan at al. in rat middle cerebral arteries and in penetrating arterioles elevated by either increasing flow or viscosity of the perfusate solution [114, 117]. We have also found similar results in MCA, i.e. the magnitude of constriction could be plotted as a function of WSS (unpublished observation). However, there are theoretical considerations that argue against the idea that WSS acting on the vascular endothelium is the signal in flow-induced constriction of cerebral vessels:

- **a.** If WSS is sensed, how does it relate to changes in CBF and cerebral blood volume (CBV)? How can a positive feed-back mechanism “serve” a negative feed-back mechanism i.e. autoregulation? Because constriction increases WSS further, it should result in further constriction of cerebral vessels, then further increase in WSS (positive feed-back manner), while CBF and CBV would decrease continuously. Such changes in CBF and CBV have not been observed, however.
- **b.** Bryan at al. and other previous studies found that constriction of cerebral vessels to flow is independent of the presence of a functioning endothelial layer [112, 114, 117], and mechanisms responsible for the constriction are localized into the smooth muscle layer of cerebral arteries. This finding also argues against that WSS is the signal. The intriguing question is: how can WSS be sensed by the smooth muscle if the flowing blood is in contact with the intraluminal side of endothelium and not with the smooth muscle? Bryan at al. proposed, that the endothelium plays a role in attenuating the shear stress-induced constrictions by an unknown dilating factor, by a dilating process, or by attenuating the mechanical force of the WSS as it is transmitted to the abluminal side of the vessel [117]. This dilator mechanism may be present, but it needs further experimental support. This could be NO, since inhibition of NOS in zero flow conditions reduced the diameter of cerebral vessels [117, 118].

c. One can assume that WSS is sensed by the smooth muscle through interstitial flow driven by the transvascular pressure difference, which was shown to be capable to cause smooth muscle constriction [119]. This idea is supported by the findings that integrins play a role (as sensors) in interstitial flow-related mechanotransduction and blocking integrins inhibits the flow-induced constriction of cerebral arteries [112, 114, 119]. This hypothesis could also explain why intact endothelium attenuates flow-induced constriction, because in case of endothelial injury or denudation the magnitude of transvascular flow is much greater than in intact arteries [119].

It is of note however, that significant amount of fluid cannot leave the vessels in the closed cranium. Although, it is unlikely that larger amount of fluid would leave the wall of larger vessels due to the presence of well developed internal elastic lamina and several layers of smooth muscle cells [52, 120]. Moreover, the amount of transmural fluid movement is likely to be minimal, because of the tight connections between endothelial cells [121]. Thus it is unlikely to lead to “leakiness” or increased filtration of plasma into the brain parenchyma. Nevertheless, the exact nature of the “transmural fluid signal” proposed by Tarbell et al. [119] still remains obscure.

d. Flow velocity increases as diameter decreases if flow (and pressure) constant. Flow velocity itself could be a candidate for the trigger parameter, as it is related to changes in CBF and CBV, but it is difficult to envision a sensor for flow velocity, since velocity is not a force that can be sensed by cells.

e. Another possibility is that increasing flow (mass transport) washes in or out vasoactive substances providing a tonic effect on vascular smooth muscle. For instance, NO has been proposed to perform a tonic dilator effect on cerebral vessels [29, 117, 118]. We have also shown a significant reduction in basal diameter of cerebral vessels when NOS was inhibited. It is also known that NO can inhibit the production of 20-HETE [122], which was shown to mediate flow-induced constriction of cerebral arteries [23]. Thus, hypothetically a decreased effect of NO could lead to an enhanced constrictor effect of 20-HETE. Reactive oxygen species were also shown to play a role in flow-induced constriction in rat middle cerebral arteries [23], and they can be also potential candidate to decrease the bioavailability of NO leading to enhanced 20-HETE production. Endothelial-derived dilator arachidonic acid metabolites by lipoxygenase, epoxyeicosatrienoic acids (EETs) are also known to be produced by the endothelium in response to shear stress [123], and also they are capable to inhibit TXA_2 receptor [124] which was shown to mediate the constriction to flow by 20-HETE [23]. Thus, they could also play a role in the “wash-out” theory. However, presently existing data question these possibilities, showing that flow-induced constriction of cerebral vessels still exists in the presence of NO synthase inhibitor L-NAME and after denudation of endothelium [114, 117] and such constriction was not observed in basilar arteries instead of dilations. Also, at a constant flow rate increases in the viscosity of the perfusing solution could constrict the vessels while increased wall shear stress, as well [114].

These ideas and other controversial observations need to be addressed by future studies. Such “physiological” investigations would be very important since precise regulation of CBF has important clinical consequences to prevent and to treat headache of vascular origin, TIA, stroke, vascular cognitive impairment (and mixed vascular dementia with Alzheimer disease), edema formation after brain injury or associated with tumor formation and other fatal cerebral pathologies. Also, without knowing the exact nature of mechanical, vasomotor response only “signaling” studies would not yield valuable information.

3) Cellular and molecular signaling of flow-induced responses of cerebral vessels

In this section we briefly summarize the molecular mechanisms that are shown to play role in the flow-induced responses of cerebral vessels (Figure 3).

a) Flow-induced dilation of cerebral vessels—There are only a few data in the literature regarding the mechanisms of flow-induced dilation of cerebral vessels. In the rat basilar artery Paravicini at al. found that the dilation is mediated by H_2O_2 and NO generated by NADPH oxidase and eNOS, and PI3-K activation is important in activation of NADPH oxidase [102]. Recently Drouin at al. demonstrated, similar to Paravicini at al. that H_2O_2 mediates flow-induced dilation, but it derives from NO synthase, which is activated by an Akt-dependent pathway (Figure 3) [104, 105].

b) Biphasic response of cerebral vessels to flow—In line with the observations of flow-induced dilation, in some of the studies founding biphasic response to flow the dilation was endothelium-dependent and was blocked by inhibition of NO synthase (L-NAME) [108, 110]. Ward at al. also found that indomethacin blocked the response and proposed a role for cyclooxygenases-derived metabolites [109]. The constrictor response was found to be dependent on increases in intracellular (smooth muscle) Ca^{2+} concentration [106, 107].

c) Flow-induced constriction of cerebral vessels—Madden at al. found that administration of integrin-binding peptides, scavenging reactive oxygen species by superoxide dismutase (SOD) and inhibition of tyrosine kinase blocked the constriction suggesting that integrin signaling, free radicals and tyrosine kinase play a role in mediation of flow-induced constriction in an endothelium-independent manner [112]. Similarly Bryan at al. observed that an integrin blocker specific for β_3-integrin and SOD abolished the flow-induced constriction. They also measured Ca^{2+} concentration in the vessel wall and demonstrated that flow-induced constriction is accompanied by increases in $[Ca^{2+}]i$. Denudation of the endothelium did not affect flow-induced constriction [114, 117].

Recently we have found that flow-induced constriction of cerebral vessels was blocked by inhibition of 20-HETE synthesis, TXA_2 (TP) receptor, COX activity and scavenging ROS. Therefore we proposed that increases in flow activate arachidonic acid cascade, and the metabolites are further metabolized by cytochrome P450 4A enzymes (CYP450 4A) into 20-hydroxieicosatetraenoic acid (20-HETE). It is known that CYP450 4A also produces reactive oxygen species (ROS), which contribute to the constriction. Thus it seems that flow-induced constriction of MCA and that of human cerebral arteries is mediated by 20-HETE via thromboxane A_2/prostaglandin H_2 (TP) receptors and requires COX activity (Figure 3) [23].

4) Physiological significance of flow induced responses of cerebral vessels of different sizes and regions. Implications for heterogeneity of autoregulation

From the observed responses one can estimate the change in CBF by using diameter values induced by only changes in pressure and then simultaneous changes in pressure and flow using the Hagen–Poiseuille equation [23]. Also, a “gain factor (G)” can be calculated indicating the strength or efficacy of the autoregulation of blood flow (G = 1 indicates perfect autoregulation, whereas G<1 means inefficient autoregulation, when CBF increases as a function of intraluminal pressure) [22, 23]. In case of flow-induced constriction we found that simultaneous increase of pressure+flow enhanced the only pressure-induced decrease in diameter Also, the gain of autoregulation (G) calculated using diameters induced by pressure alone was below 1, whereas G was ≈1 when pressure+flow were increased simultaneously indicating a more efficient autoregulation. When only pressure was increased estimated CBF showed a linear increase, but when pressure+flow increased

simultaneously estimated CBF decreased significantly and remained relatively constant [23]. Based on this we propose that in the circulatory areas where vessels constrict to flow simultaneous operation of pressure- and flow-induced constrictions is necessary to explain an effective autoregulation of CBF (Figure 2).

In the cerebrum, in the internal carotid circulatory area resistance is profoundly determined by larger arteries [18, 43, 44, 50]. In line with this, larger arteries (i.e MCA) constrict to increases in flow, flow-induced constriction enhances the pressure-induced tone of cerebral vessels leading to a more efficient autoregulation of CBF, and via this flow-induced constriction of cerebral arteries plays a role in regulating cerebral blood volume and intracranial pressure. Therefore, in addition to myogenic response, flow-induced constriction (or dilation) may also participate in the development of segmental resistance of the cerebral circulation, because both large arteries and arterioles respond to changes in flow with either constriction or dilation [23, 100, 105–107, 110, 114, 125].

This segmental vascular resistance is thought to provide constant blood flow when blood flow is altered locally (for example due to metabolic factors), and to protect downstream brain circulation from pressure and volume overload [43, 50, 52]. Regarding flow-induced responses the importance of segmental function of cerebrovascular resistance and the role of large arteries are underlined by the findings of Fujii at al. and Garcia-Roldan and Bevan [106, 110] showing that isolated cerebral arterioles constricted when pressure or flow rate is high and dilated when they are low.

Also, the vasomotor tone “set” by the two hemodynamic forces can be modulated or overridden by other factors sensitive to the needs of neural tissues. Whereas flow-induced constriction may play an important role (together with the pressure sensitive myogenic tone) in regulation and maintenance of cerebral volume and intracranial pressure, local neural needs can increase cerebral blood flow regionally via neural, glial and other regulatory mechanisms, which can also be propagated to upstream vessels [1, 17]. This concept is in line with the suggestion of studies showing that metabolic dilation could overcome the constrictor effect of pressure or flow [23, 112, 126, 127]. Conversely, in the brain stem (vertebro-basilar system) arterioles are the major site of resistance [50, 51], thus larger arteries, such as the basilar artery “can” dilate to flow participating in reactive hyperemia [125]. The heterogeneity of autoregulation is likely due to the different efficacy of pressure and flow sensitive vascular mechanisms and/or contribution of metabolic mechanisms and neurovascular coupling. The proposed concept should be further clarified in the future by in vitro investigation and comparison of pressure- and flow-induced responses of cerebral arteries and arterioles from different regions of cerebrovascular tree [128]. More importantly, in vivo imaging of CBF in experimental animals and humans could be performed by means of MRI, laser speckle imager and other novel techniques in order to clarify the mentioned concept of the role of hemodynamic forces in regulation of CBF, in which pharmacological intervention of signaling mechanisms may reveal further detail of autoregulation of CBF.

All in all, regulation of cerebral blood flow (CBF) is the result of multilevel, interacting complex mechanisms to maintain an appropriate blood flow providing nutritional and gas supply for the brain tissue. To simplify, the tone of cerebral vessels is affected by both intraluminal pressure-induced constriction and flow-induced dilation or constriction, “setting a basal vasomotor tone”, which is then modulated by metabolic, astrocytic-glial, neural signals providing the complex multilevel regulation of CBF. The sum of these mechanisms is capable to match the requirement of maintaining an appropriate blood flow for the brain tissue and in the same time complying with the limited space in the closed cranium.

5) Pathophysiological and clinical relevance of pressure- and flow-induced autoregulatory mechanisms of CBF

Changes in hypertension—Previous studies described that myogenic responses of cerebral vessels is enhanced in hypertension [22, 63, 129, 130]. Logically it is considered to be an adaptation extending the range of CBF autoregulation to higher systemic blood pressure. Based on our recent concept described in this review (Fig 2) enhanced flow-dependent constriction may also contribute to the functional adaptation of cerebral vessels to hypertension in order to "protect" brain tissue and intracranial space from high pressure and volume. Indeed, flow-induced constriction seems to be enhanced in hypertension [131], and mediated by upregulation of 20-HETE signaling (Toth et al 2012, manuscript in preparation). This could be due to the chronic elevation of blood flow due to the greater pressure drop across the cerebral circulation in hypertension.

Possible contribution to stroke and other cerebrovascular disorders—As mentioned above, myogenic response is enhanced in hypertension protecting the cerebral circulation from higher blood pressure. The importance of this mechanism was demonstrated by Smeda at al showing that that the enhanced myogenic response of rat cerebral arteries is attenuated before and lost after the onset of cerebral hemorrhage [132, 133]. Parallel with the myogenic response we found that enhanced flow-induced constriction in hypertension is attenuated before and lost after the onset of hemorrhagic stroke in stroke prone spontaneously hypertensive rats (unpublished observation, Toth P at al., 2011). On the other hand enhanced constriction to flow in hypertension can cause decreased capability to adapt to decrease in blood pressure probably contributing to ischemic damage of the brain. This idea is supported by the findings that inhibition of 20-HETE production reduces significantly the infarct size after middle cerebral artery occlusion [134–136]. However, all of these ideas need to be investigated in the future.

Summary

Although autoregulation of cerebral blood flow at higher pressures has been explained solely by the pressure sensitive myogenic mechanism, more and more data show that it is insufficient to do so. Because during changes in pressure flow changes as well, it is logical to assume that changes in flow also has a role. Probably this was the reason for conducting many studies to elucidate the nature, the underlying mechanisms and physiological importance of flow-induced responses of cerebral vessels in the last 30 years. These studies showed that increases in intraluminal flow is sensed by the vascular tissues of cerebral vessels and converted into changes in diameter: constriction, dilation or biphasic response. It seems that the nature of response depends on the region of the brain, or vascular segment, size or localization. Also, species and gender differences cannot be ruled out. These differences are likely to have physiological role by modulating myogenic mechanism and regulation of CBF and CBV and intracranial pressure, and at the same time, providing an appropriate amount of blood flow to the brain tissue according to the needs.

Although the precise signaling of mechanotransduction of flow signal is not yet known, arachidonic metabolites, especially 20-HETE, nitric oxide, potassium and TRP channels seem to play important role. In addition reactive oxygen species produced by these and other enzymes, such as NAD(P)H oxidase may also contribute to the modulation of vasomotor tone.

It is clear however, that there are still many controversial observations, unexplained signaling and unknown mechanisms that could all contribute to the diameter response of cerebral vessels of different size and origin to changes in hemodynamic forces and thus regulation of cerebral blood flow. Because cerebrovascular diseases (stroke, vascular

dementia, cognitive impairment, aging etc.) associated with the impaired regulation of CBF are still leading causes of human morbidity and mortality it is imperative to further investigate the responses and the underlying mechanism of cerebral vessels to hemodynamic/rheological forces.

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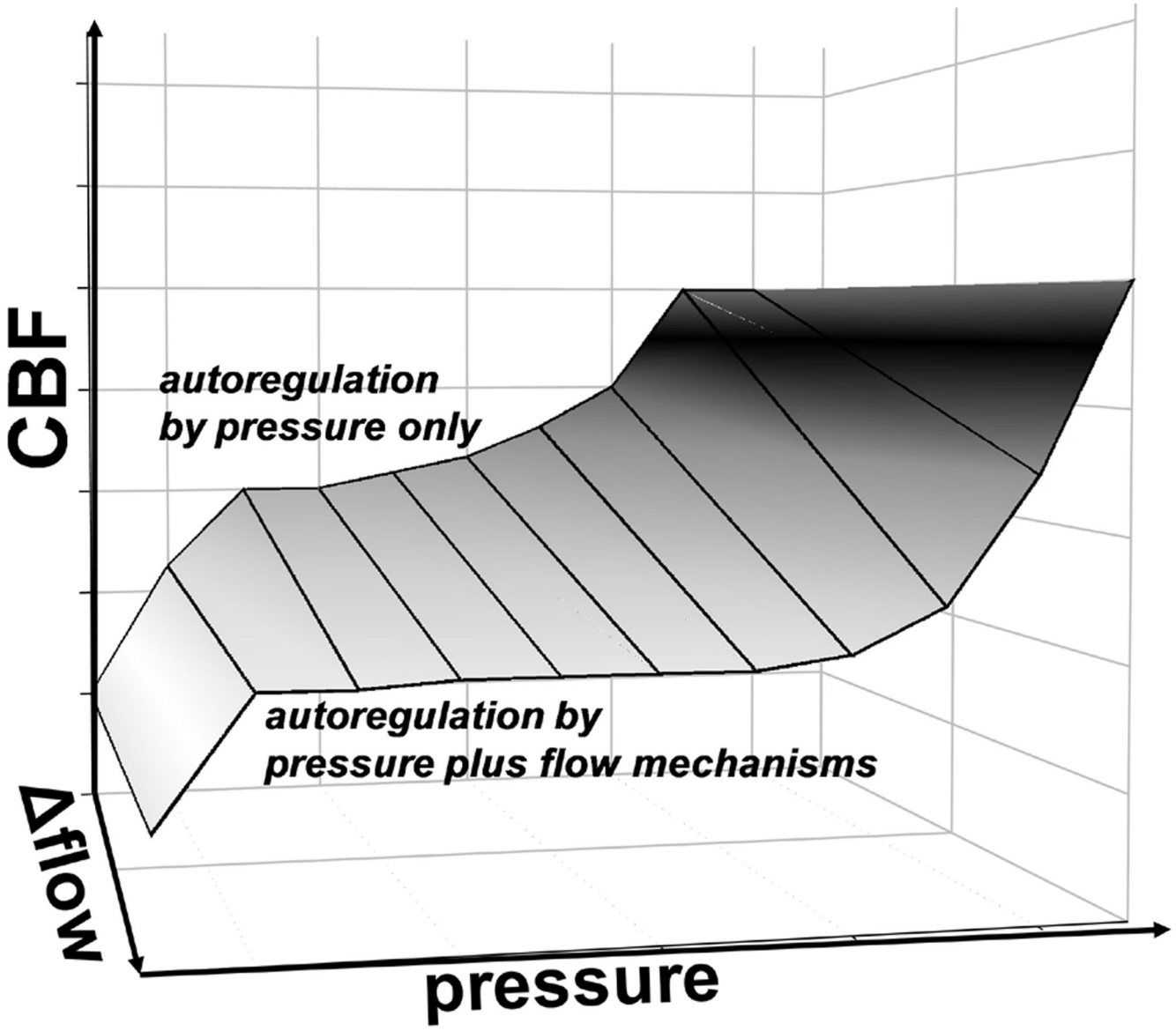

Figure 1.

Changes in diameter (μm) of an isolated middle cerebral artery and a basilar artery to changes in intraluminal flow as a function of time, redrawn from original traces (P. Toth). In this experimental conditions flow is generated by increasing intraluminal pressure differences (Δ5, Δ10, etc, mmHg) via the vessel by changing the inflow and outflow pressures with the same amount, but in the opposite directions (see details of methods in Toth, P. at al [23]). The opposite diameter responses indicate important regional differences in the nature of flow-induced responses of cerebral arteries. Constriction of middle cerebral artery by increasing cerebrovascular resistance (CVR) contributes to the autoregulation of cerebral blood flow by the “pressure-flow” mechanisms and thereby to the overall regulation of intracranial volume and pressure. In contrast, dilation of the basilar artery to increases in flow, similar to other peripheral vessels contributes to the development of functional hyperemia. See detailed discussion in the text.

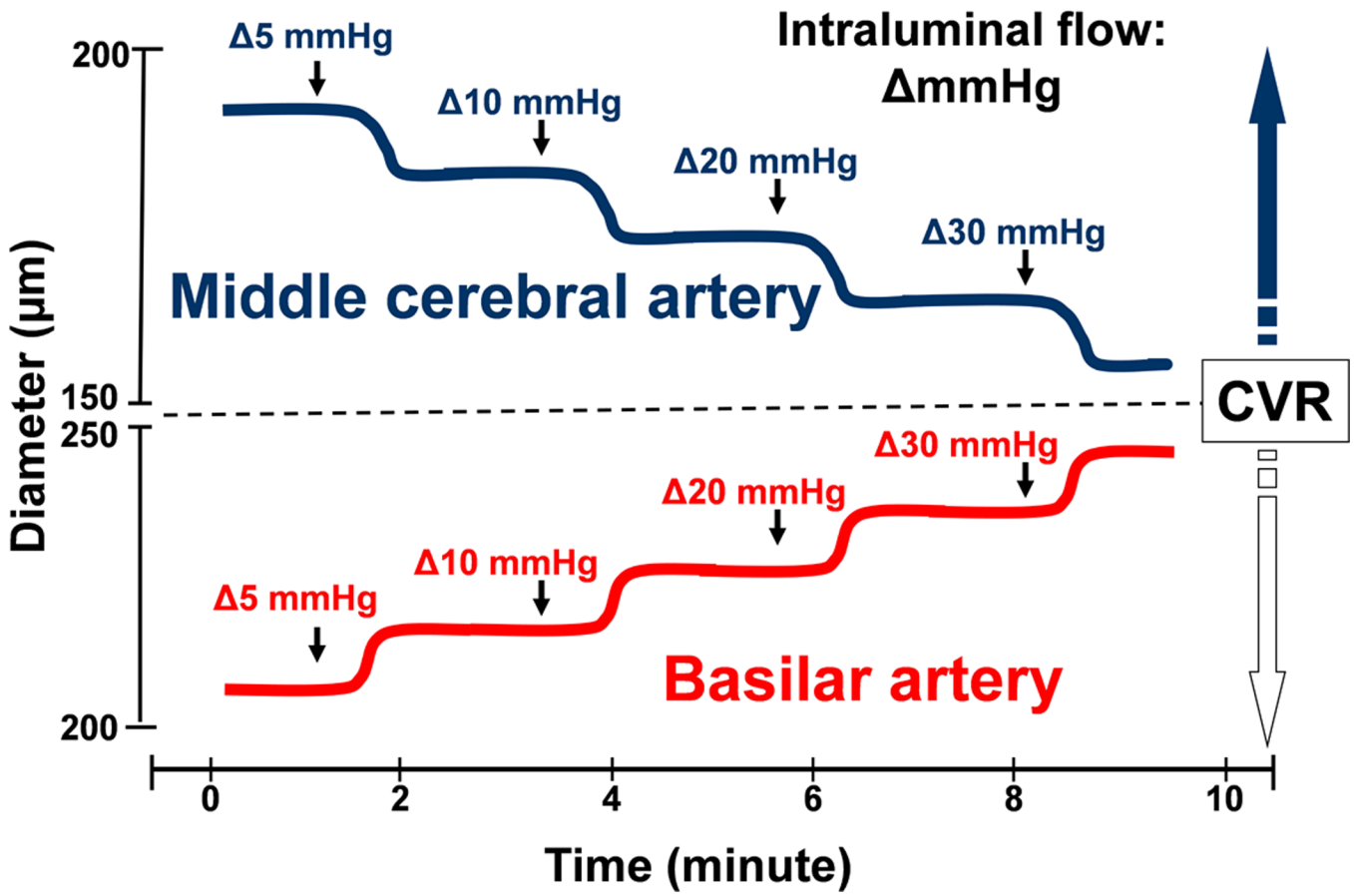

Figure 2.

Schematic diagram showing the proposed physiological role of flow-induced constriction of cerebral arteries in autoregulation of cerebral blood flow. Combined effect of changes of intraluminal pressure and intraluminal flow (Δ flow) achieves a more effective autoregulation of cerebral blood flow (CBF), whereas only pressure-induced diameter responses still allow substantial increases in CBF, thus inefficient autoregulation. It is likely that in vivo the “plateau” of autoregulation is not perfectly flat, i.e. the gain is less than 1, thus there is a slight increase in CBF as systemic pressure increases. Nevertheless, it is effective enough to prevent an exponential increase of CBF. Also, the range and shape of autoregulatory curve is likely to be more “rounded” at low and high pressure values.

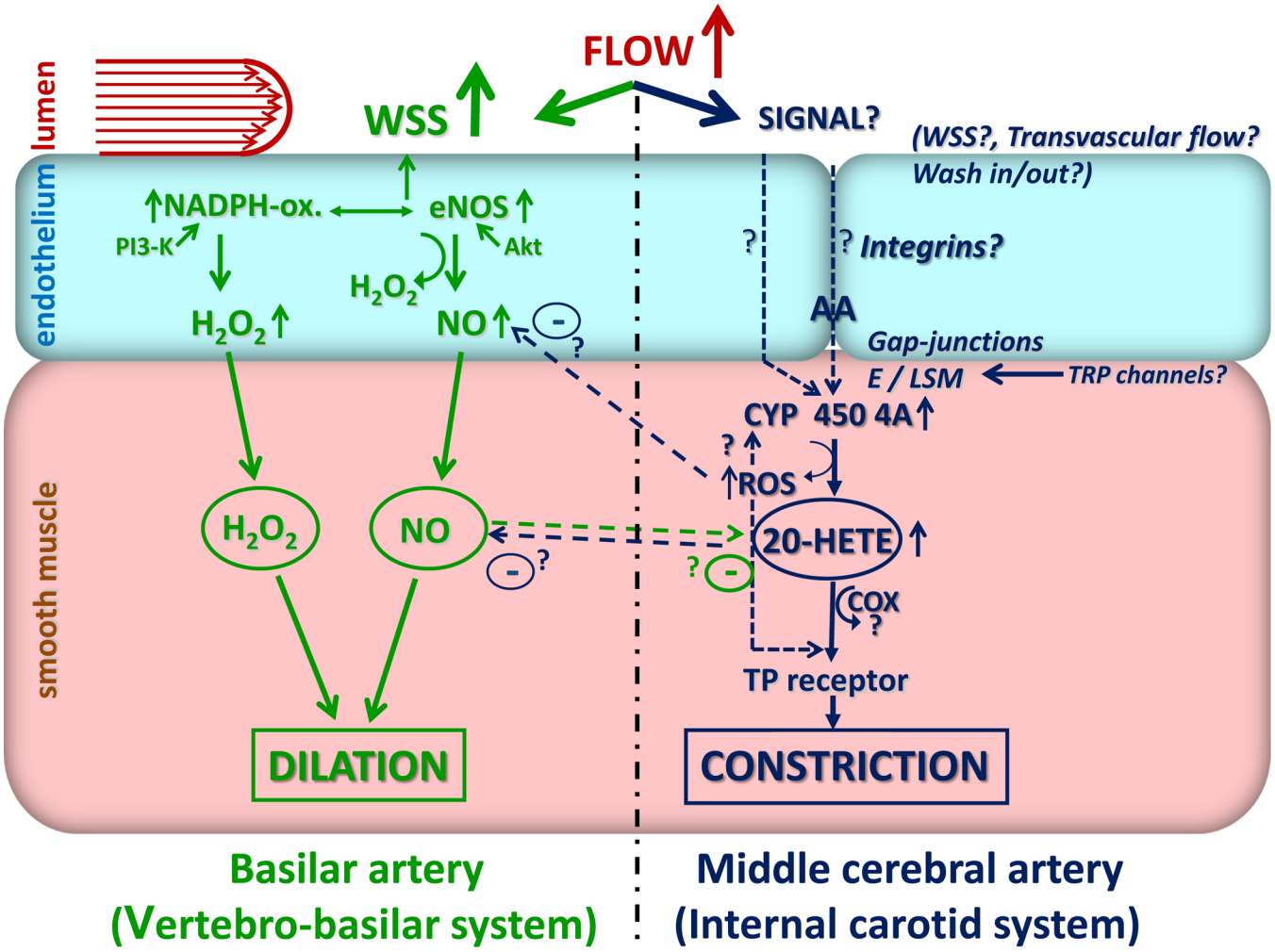

Figure 3.

Proposed intracellular and molecular mechanisms eliciting flow-induced responses of cerebral vessels. Flow induces dilation, biphasic responses, or constriction of cerebral vessels depending on the regional and segmental localization of the vessels. We propose that in the internal carotid system larger arteries (such as the middle cerebral artery) constrict to increases in flow. The flow-induced constriction is mediated by 20-hydroxyeicosatetraenoic acid (20-HETE) (a metabolite of arachidonic acid (AA) produced by cytochrome P450 4A enzymes (CYP450 4A) acting via thromboxane A_2/prostaglandin H_2 (TP) receptors and requires COX activity. CYP450 4A also produces reactive oxygen species (ROS), which contribute to the constriction. Whereas, in the brain stem supplied by the vertebro-basilar system larger arteries, such as basilar artery, dilate to flow. Dilation is mediated by NADPH-oxidase (activated by phosphatydilinositol3-kinase (PI3-K) derived H_2O_2 and/or eNOS derived nitric oxide (NO). eNOS is activated in an Akt-dependent pathway, and probably generates H_2O_2, as well (ref number here!! based on Toth at. al, Paravicini at al. and Drouin at al.). The exact nature of signals and sensors are still unknown (see detailed description in the text).