

Why is the neural control of cerebral autoregulation so controversial?

Philip N. Ainslie^{1*} and Patrice Brassard^{2,3}

Addresses: ¹Center for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia – Okanagan, Kelowna, British Columbia, Canada; ²Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, Canada; ³Research Center of the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada

* Corresponding author: Philip N. Ainslie (philip.ainslie@ubc.ca)

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Abstract

Cerebral autoregulation refers to the mechanisms that act to keep cerebral blood flow (CBF) constant during changes in blood pressure. The mechanisms of cerebral autoregulation, especially in humans, are poorly understood but are undoubtedly multifactorial and likely reflect many redundant pathways that potentially differ between species. Whether sympathetic nervous activity influences CBF and/or cerebral autoregulation in humans remains controversial. Following a brief introduction to cerebral autoregulation, this review highlights the likely reasons behind the controversy of the neural control of cerebral autoregulation. Finally, suggestions are provided for further studies to improve the understanding of the neural control of CBF regulation.

Introduction

The human brain has a limited capacity for substrate storage and a high metabolic rate, making the precise regulation of CBF critical for the maintenance of constant nutrient and O₂ supply [1,2]. While the brain represents ~2% of body weight, it receives up to 15–20% of total cardiac output. The brain is thus one of the most highly perfused organs in the body. Indeed, the elevated metabolic requirements of the brain, which relies to an important extent on oxidative metabolism, necessitate a great proportion of cardiac output. Blood flow to the brain, however, needs to be relatively constant since it is enclosed by an inflexible structure, the skull, which does not allow for the expansion of extracellular fluid or tissue. Vasogenic edema induced by cerebral swelling can elevate intracranial pressure, leading to severe neurologic complications and even death. Water and solute transport from the blood into the brain parenchyma is controlled in different ways, taking into consideration the importance for the brain to preserve intracranial pressure within normal ranges and also to provide an appropriate ionic milieu for neuronal function. In addition, the large arteries play a more significant role

in vascular resistance in the brain versus other vascular beds, making the cerebral circulation distinctive from the peripheral circulation. This noticeable role of large arteries in vascular resistance is most likely of importance in providing relatively constant blood flow to the brain and defends the microcirculation against surges in blood pressure.

The general agreement that products of cerebral tissue metabolism and chemical stimuli (i.e. arterial carbon dioxide tension [PaCO₂]/pH) are among the key factors that influence the diameter of the cerebral vessels and, as a consequence, cerebrovascular conductance/resistance and blood flow of the brain. Moreover, another group of regulatory components—neural stimuli—may be involved in the control of the cerebral vessel caliber and brain blood supply. The neural contribution has been controversial ever since the first description of perivascular nerve fibers in the walls of brain vessels [3-5]. In this short review, not all aspects of the unique cerebral circulation will be covered; rather, we focus on the likely reasons behind the controversy of the neural control of cerebral autoregulation. Suggestions are then provided for further

studies to improve the understanding of the neural control of CBF regulation.

Cerebral autoregulation: an overview

Cerebral autoregulation refers to the mechanisms that act to maintain CBF constant during changes in blood pressure. Although the physiological underpinnings remain obscure, cerebral autoregulation is often characterized as being either a static or dynamic component. Static versus dynamic cerebral autoregulation is an experimental, not a physiological, distinction where static cerebral autoregulation is typically described as operating over several minutes to hours and represents the steady-state relationship between mean arterial pressure (MAP) and CBF. In contrast, dynamic cerebral autoregulation commonly refers to the cerebral pressure–flow relationship as observed during transient changes in MAP (e.g. with changes in posture), taking place over a period of seconds. Although these two metrics act on a continuum, the brain circulation seems to be better at buffering lower frequency fluctuations in blood pressure (<0.20 Hz), than higher frequency fluctuations (>0.20 Hz). To our knowledge, there are no data that explicitly indicate that the short- and long-term regulation of CBF—dynamic and static cerebral autoregulation, respectively—are separate mechanistic entities (reviewed in [6]), although it could represent the same mechanism(s) if cerebral autoregulation is considered to be a high-pass filter. However, we note that in some specific conditions, both may dissociate, for example, in sepsis [7] and in patients with type 2 diabetes [8]. Nevertheless, in contrast to dynamic cerebral autoregulation (reviewed in [6,9]), the mechanisms of static cerebral autoregulation have been studied less and warrant further investigation.

Cerebral autoregulation: the role of sympathetic nervous activity?

The mechanisms of cerebral autoregulation are not entirely understood and may even differ with elevations versus decrements in blood pressure (see section “Asymmetry and influence of perfusion pressure” below). Whether the sympathetic nervous activity (SNA) influences CBF and/or cerebral autoregulation in humans remains controversial [10,11]. The brain circulation is richly supplied by perivascular adrenergic nerves [12], and smooth muscle cells in the arterioles have alpha- and beta-adrenergic receptors [13]. The well-controlled animal studies that have investigated the influence of SNA on CBF have reported a reduced CBF at baseline as well as during acute hypertension with the stimulation of the superior cervical ganglion [2,14]. In dogs, using an isolated dual preparation that eliminated baroreceptor and chemoreceptor responses to large blood pressure changes, it was shown that when the carotid sinus nerves

were cut, autoregulation was completely abolished [15]. In contrast, cerebral autoregulation has been reported to be preserved in sympathetically and parasympathetically denervated animals (cats), which suggest that SNA does not have a major role for cerebral autoregulation [16]. In humans, there exists biochemical evidence suggesting that SNA influences CBF [17], although it seems to exert a trivial influence on CBF in comparison to its role on many other regions of the peripheral circulation. Nevertheless, at least based on transcranial Doppler (TCD) measures, findings in humans support a modest and somewhat frequency-dependent role of SNA [18-20] and parasympathetic nervous activity [21,22] as having an influence on dynamic cerebral autoregulation. Advantages and limitations relating to the experimental approaches to assessing cerebral autoregulation in humans have been recently reviewed [6].

Interestingly, neuronal nitric oxide has the potential to modulate cerebral autoregulation, at least in animal models. This suggests that, while extrinsic innervation may not be a key player in cerebral autoregulation, intrinsic innervation may be important [23]. Nevertheless, the picture is not that clear in humans. Patients receiving L-NMMA, a non-selective nitric oxide synthase inhibitor, presented with an attenuated dynamic cerebral autoregulation characterized by an autoregulatory index featuring a transient decrease in arterial blood pressure that is induced by the rapid release of bilateral thigh cuffs. Interestingly, the same dynamic cerebral autoregulation metric was preserved in control patients, with administration of a comparable pressor dose of noradrenaline [24]. However, L-NMMA did not affect dynamic cerebral autoregulation measured by transfer function analysis in the low frequency range in healthy volunteers [25]. Thus, a role of nitric oxide in human studies (at least via L-NMMA utilization) has shown an unremarkable influence on cerebral pressure-flow relationships.

It has been suggested that the byproducts of metabolism, such as H⁺, K⁺, O₂ and adenosine, also have a function in cerebral autoregulation [26]. The cerebral smooth muscle’s myogenic behavior, which constricts in response to elevated blood pressure and dilates in response to decreased blood pressure, is also likely responsible for cerebral autoregulation [27,28]. Recent evidence in humans supports a modest and frequency-dependent role of a myogenic mechanism in dynamic cerebral autoregulation [29].

Why is the neural control of CBF so controversial?

Clearly, the mechanisms underpinning cerebral autoregulation are multifactorial and likely reflect many redundant

pathways that potentially differ between species. Nevertheless, the obvious question arises: why is the neural control of CBF and hence cerebral autoregulation so controversial? We explore the likely reasons below.

Redundancy

In an intact animal or human, redundant mechanisms operate to govern the behavior of a complex system (e.g. to maintain hemostasis) [30]. For example, a number of dilator factors, such as prostanoids, nitric oxide and histamine, can counteract the constrictor effects of noradrenaline in the cerebral circulation [31,32].

Heterogeneous distribution of sympathetic innervation

Variations in sympathetic innervation density are heterogeneous and suggestive of preferential sympathetic effects in certain areas of the brain. In addition, arterioles have both alpha- and beta-adrenergic receptors [13] that also differ in density depending on the size of the vessel.

Blood-brain barrier permeability

The blood-brain barrier protects the brain from circulating neurotransmitters, especially catecholamines [33]. However, the experimental model used to examine this question, and its impact on blood-brain barrier permeability, may lead to opposite findings. For instance, another obvious consideration in humans is that the use of adrenergic blockade is confounded by direct cardiac (beta, e.g. [22,34]) and peripheral vascular (alpha, e.g. [19,35]) effects. Furthermore, these drugs may not similarly affect the cerebral vasculature due to their inability to cross the blood-brain barrier.

Species divergences

Species divergences are clearly varied in cerebrovascular responsiveness to sympathetic nerve stimulation. The number of sympathetic alpha- and beta-adrenergic receptors in different cerebral regions and in different species is variable (for review see [36]). Moreover, in several species, there are developmental changes in the cerebrovascular responsiveness to alpha-adrenoceptor-mediated stimuli [37,38].

Duration and intensity of sympathetic stimulation

The duration and nature of the stimulation may also influence the cerebrovascular response. For example, the cerebral circulation may escape from the sympathetic stimulation over a 5±7-minute period [39]. In other words, a "vasomotor escape" phenomenon occurs during sustained sympathetic activation, suggesting that the neural control of the cerebral circulation may be more effective under dynamic than steady-state conditions. The use of nonphysiological frequencies (1–50 Hz) that are coupled to the different patterns of stimulation used

in animal studies makes these findings difficult to extrapolate to humans. Of note, the intensity (i.e. magnitude) of SNA or blood pressure activation is also important for the cerebrovascular response (reviewed in [6,9]).

Asymmetry and influence of perfusion pressure

Recent evidence in both humans [40–42] and animals [43] supports the idea of hysteresis in the dynamic cerebral pressure-flow relationship. In other words, the brain can effectively buffer acute hypertension better than acute hypotension. In addition, it seems like the effect of sympathetic stimulation is dependent on the actual arterial pressure. Indeed, sympathetic stimulation has larger effects during arterial hypertension compared to normotensive conditions [44,45].

Regional differences in cerebral autoregulation

Cerebral autoregulation has typically been studied in the middle cerebral artery (MCA), assuming that variables of interest (cerebral autoregulation, cerebrovascular reactivity to CO₂, etc.) will be identical in other cerebral arteries. Some recent reports suggest that it is not the case. For example, dynamic cerebral autoregulation, characterized by the rate of regulation during head-up tilt, is attenuated in the vertebral artery but not in the internal carotid artery [46]. The posterior cerebral artery also seems to have a less effective dynamic cerebral autoregulation characterized by transfer function analysis, compared to the MCA [47]. However, studies have also reported similar dynamic cerebral autoregulation in the MCA and vertebrobasilar circulation during supine rest [48] and orthostatic stress [49]. White matter seems to have a faster recovery compared to gray matter, while the cerebral cortex exhibits faster recovery compared to the cerebellum following thigh cuff release [50]. New technologies permit a more integrative evaluation of the cerebrovascular function in response to different challenges. Future studies need to consider regional differences in CBF regulation during blood pressure manipulations.

Metabolic restraint

Brain metabolism governs local changes in cerebral perfusion (cerebral metabolic rate for oxygen [CMRO₂ in mmol·100g·min⁻¹] = global CBF [mmol·100g·min⁻¹]·[CaO₂-CvO₂], CaO₂ and CvO₂ represent arterial and venous oxygen content, respectively) and possibly contributes to global CBF changes during different physiological situations, such as sleep [51], anesthesia [52] or exercise [53]. Brain metabolism is also negatively affected in numerous pathological brain conditions [54] as well as after stroke [55]. This being acknowledged, how prevailing cerebral metabolism might affect cerebral autoregulation in healthy humans remains unknown. This consideration is particularly important in comparing studies conducted

during wakefulness to those during sleep or anesthesia. Moreover, a metabolic restraint on the capacity of the sympathetic nervous system to provoke vasoconstriction has been reported during exercise in skeletal muscles [56]. Indirect evidence of such metabolic restraint, or sympatholysis, has been reported in healthy humans receiving phenylephrine at rest and during moderately intense exercise [57]. This evidence supports animal model data [58]. Since resting brain metabolism is elevated compared to skeletal muscle metabolism, it could be speculated that sympatholysis could attenuate the influence of SNA on CBF during everyday activities.

Conclusions and future directions

This short précis summarizes past and current findings in the context of cerebral autoregulation. We intentionally focused on one of the most controversial mechanisms of cerebral autoregulation: neural control. Rather than summarizing the canalized view that the role of SNA on CBF and/or cerebral autoregulation in humans remains controversial, we focused on the likely reasons behind this controversy. Aspects related to redundancy, heterogeneous distribution, blood-brain barrier permeability, species differences, variation in the duration and intensity of sympathetic stimulation, asymmetry and influence of perfusion pressure, regional differences in cerebral autoregulation and metabolic constraint were some of the likely factors leading to the variable nature of reports in the human and animal literature. Understanding and appreciating these complexities is imperative to improve understanding of the physiologic role of SNA in cerebral autoregulation. In order to further examine this fascinating and important research area of CBF regulation in humans, we consider that the next step is to conduct a definitive, within-subjects assessment of global and regional CBF across a range of non-pharmacologically and pharmacologically perturbed blood pressures with maintained PaCO₂. Additionally, it seems essential not to rely solely on TCD for these types of questions and to incorporate imaging modalities and directly modify cerebral SNA outflow (not just global SNA) to elucidate its role in cerebrovascular control. One way to accomplish this is via a centrally acting alpha-2 adrenoreceptor agonist (e.g. clonidine) and quantify the question of whole body versus cerebral SNA using noradrenaline spillover methods [17].

Abbreviations

CBF, cerebral blood flow; MAP, mean arterial pressure; MCA, middle cerebral artery; SNA, sympathetic nervous activity; TCD, transcranial Doppler.

Disclosures

The authors declare that they have no disclosures.

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