Mechanisms of cerebrovascular autoregulation and spreading depolarization-induced autoregulatory failure: a literature review

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Abstract: Cerebrovascular autoregulation maintains brain hemostasis via regulating cerebral flow when blood pressure fluctuation occurs. Monitoring autoregulation can be achieved by transcranial Doppler ultrasonography, the pressure reactivity index (PRx) can serve as a secondary index of vascular deterioration, and outcome and prognosis are assessed by the low-frequency PRx. Although great changes in arterial blood pressure (ABP) occur, complex neurogenic, myogenic, endothelial, and metabolic mechanisms are involved to maintain the flow within its narrow limits. The steady association between ABP and cerebral blood flow (CBF) reflects static cerebral autoregulation (CA). Spreading depolarization (SD) is a sustained depolarization of neurons with concomitant pronounced breakdown of ion gradients, which originates in patients with brain ischemia, hemorrhage, trauma, and migraine. It is characterized by the propagation of an extracellular negative potential, followed by an increase in O2 and glucose consumption. Immediately after SD, CA is transiently impaired but is restored after 35 min. This process initiates a cascade of pathophysiological mechanisms, leading to neuronal damage and loss if consecutive events are evoked. The clinical application of CA in regulating CBF is to dilate the cerebral arteries as a compensatory mechanism during low blood pressure, thus protecting the brain from ischemia. However, transient impairment of CBF autoregulation due to the mechanism regulated by SD autoregulation has not been reported previously. In this review, we found that SD serves as a vital factor that disrupts CBF autoregulation, and these findings provide insight into the mechanical complexities of SD-induced autoregulatory failure.

Keywords: Mechanism, cerebrovascular autoregulation, autoregulatory failure, spreading depolarization (SD)

Introduction

Recent studies have shown the association between cerebral blood flow (CBF) and metabolic biochemistry and vascular smooth muscle modifications to achieve physiological cerebrovascular homeostatic pressure [1]. The brain itself has the ability to maintain homeostasis by internal mechanisms to obtain sustained cerebral flow while blood pressure fluctuation occurs. This ability is known as autoregulation [2].

To date, there are multiple known mechanisms that all contribute to autoregulation. Four important theories have been proposed to explain autoregulation: the myogenic mechanism involving changes in cerebrovascular resistance, muscle contraction, and ionic smooth muscle interaction [3]; the metabolic mechanism involving the balance between supply and demand, CO2 concentration, and nitric oxide (NO)-mediated activation [4-6]; the neurogenic mechanism involving sympathetic neural control [7]; and the endothelial cell-related factor mechanism involving humoral stimuli [8].

Spreading depolarization (SD) involves the vascular system by driving progressive autoregulation into failure, thus leaving an altered blood flow in cerebral regions with an already increased demand of supply. This causes pronounced disruption of inherent metabolic mechanisms, altered ionic exchange and release, and disturbances in synaptic signaling with resulting neuronal loss [9].

This review aimed to highlight the importance of the intrinsic autoregulatory process in the cerebral arteries and how SD functions in autoregulatory disruption.
Cerebrovascular autoregulation

The regulation of CBF is a complex and integrated process that is related to the structures of all layers of the vessel wall, including the endothelial cell layer, smooth muscle layer, outer layer of the vessel wall, neurons and glial cells in the brain parenchyma, intracranial blood and cerebral spinal fluid (CSF), and extracellular interstitial fluid [10]. This regulation refers to the ability to preserve CBF at a relatively constant level, even in the presence of cerebrovascular perfusion pressure (CPP) fluctuations. Generally, the CPP ranges between 50-60 mmHg for the lower limit and 150-160 mmHg for the upper limit, meaning that this regulation is effective. The CBF is kept constant at 40-50 mL/100 g/min over the range of arterial blood pressures (ABPs) from 50 to 160 mmHg [11]. When the upper limit of autoregulation is broken, an increase in blood flow to the brain leads to excessive CBF to the maximum limit. When the autoregulation reaches the lower limit, the pressure cannot guarantee effective cerebral flow. However, the upper and lower limits of autoregulation are not absolute. They are affected by many factors, such as increased renin secretion, chronic hypertension (associated with increased sympathetic tone), and boundary value of perfusion pressure. Conversely, sleeping, physiological low blood pressure in athletes and hemorrhage-induced pathological hypotension, the presence of angiotensin-converting enzyme inhibitors, extended hypoxemia, or hypercarbia causes the threshold value of the blood perfusion pressure to decrease [7, 12]. Additionally, when adjusting for severe acute hypertension or low blood pressure, the CBF becomes weakened or even completely loses its regulating effect in cases of severe cerebral infarction, brain injury, and aneurysmal subarachnoid hemorrhage (SAH). The exact mechanism underlying self-regulation is unclear. Possible mechanisms include myogenic, endothelial cell-related factor, neurogenic, and “metabolism” or “fluid” mechanisms, which are more indicative of vasomotor function than metabolic regulation. These mechanisms will be discussed in more detail in this review.

Autoregulation monitoring

The applications of xenon-enhanced computed tomography (Xe-CT) made it possible to study regional CBF [13]. In recent years, single photon emission computed tomography (SPECT) and positron emission tomography (PET) methods have been widely used to measure CBF [14, 15]. Current commonly used methods are the N_2O measurement method, radioactive nuclide, SPECT, PET, and transcranial Doppler ultrasonography (TCD). Among them, TCD has been widely used for cerebral autoregulation (CA) assessment in the clinic for its for its mobility, low cost, real-time monitoring, and non-invasive approach. TCD has the advantages of being performed in bed or during an operation. TCD can measure CBF velocities in large intracranial vessels, immediately visualizes vascular flow, and detects dynamic changes of the flow, without anatomical imaging [16].

Pressure reactivity index

The pressure reactivity index (PRx) is a moving correlation coefficient of mean arterial pressure and intracranial cerebral pressure, reflecting the tone response of the vascular smooth muscle due to changes in transmural pressure, and it is useful as a secondary index of vascular deterioration [17]. When this association is high, it reflects disturbed autoregulation by a nonreactive behavior of the cerebral vessels. It records changes within 20 s to 2 min in frequencies between 0.05-0.008 Hz and has been used to define the autoregulation-oriented optimal cerebral perfusion pressure (CPP), at which the patient should be treated. Patients with a mean CPP close to the optimal CPP are likely to have a favorable outcome than those patients whose CPP is distant from the optimal CPP [18].

Low frequency pressure reactivity index

The autoregulation index of low frequency pressure reactivity (L-PRx) measures values by-the-minute, instead of by-the-second, of changes in vasoreactivity and the level of disturbance in vascular responses. It records frequencies of 0.016-0.0008 Hz, with a moving time window of 20 min, mainly for outcome prognosis [19].

Cerebrovascular myogenic mechanism of autoregulation

Pressure induces an increase in the smooth muscle cell membrane potential, which most likely occurs by modification of the activity of the ATP-sensitive and calcium (Ca^{2+})-activated potassium channels in the plasma membrane.
The rate of potassium leakage from cells to the extracellular space is regulated by plasma membrane potassium conductance and is the primary determinant of resting membrane potential [20]. The precise mechanism of the mechanochemical coupling is unknown. However, it has been shown that the membrane potential regulates the intracellular Ca\(^{2+}\) concentration through voltage-gated Ca\(^{2+}\) channels. The intracellular Ca\(^{2+}\) concentration is the principal regulator of smooth muscle cell tone by Ca\(^{2+}\)/calmodulin myosin light chain kinase-mediated phosphorylation of the regulatory light chains of myosin, with subsequent interaction of actin and myosin. The sequence is endothelium-independent, and the arterial constriction in response to luminal pressure is an intrinsic myogenic reflex [20].

The changes of pressure are accompanied by changes of flow; therefore, the in vivo responses of the cerebral vessels to hemodynamic changes are most likely a combination of pressure- and flow-induced mechanisms [21-24]. Thus, one can hypothesize that changes in flow contribute to the CA of CBF. In other words, when systemic pressure changes in vivo, then the diameter of the cerebral vessels correspondingly changes as well; thus, changes of CBF are determined by the combined effects of both pressure and flow.

A comprehensive model for myogenicity that consists of three interrelated but distinct phases has been proposed by Osol et al.: 1) The initial development of myogenic tone (MT); 2) Myogenic reactivity (MR) to subsequent changes in pressure; and 3) Forced dilatation (FD) at high transmural pressures. The three phases span the physiological range of transmural pressures (e.g., MT, 40-60 mmHg; MR, 60-140 mmHg; FD, > 140 mmHg in the cerebral arteries) and are characterized by distinct changes in cytosolic calcium, which do not parallel arterial diameter or wall tension, and therefore suggest the existence of additional regulatory mechanisms [25].

**Cerebrovascular metabolic mechanism of autoregulation**

One of the pathways for metabolic regulation may lie in venular-arteriolar communication [26] of carbon dioxide (CO\(_2\)). Venous CO\(_2\) produced by metabolism can diffuse to the arterioles, governed by a time constant of the order of 20 s [27]. The arteries have the capacity to react either by dilatation or constriction when a stimulus such as CO\(_2\) takes in place. When an elevated arterial blood CO\(_2\) pressure flows into the capillaries and diffuses into the interstitial fluid, the blood flow set point increases. As an increase in capillary pressure increases capillary blood flow until a new constant state is reached, this is the outcome of CBF under hypercapnic conditions. A small increase in capillary O\(_2\) is also expected due to the interaction between CO\(_2\) and oxyhemoglobin dissociation; therefore, by this expected increase, the CBF decreases and the O\(_2\) extraction fraction remains constant [28].

Other studies have shown that in human and rat cerebral arteries, (1) an increase in flow elicits constrictions; (2) a signaling mechanism of flow-induced constriction of the cerebral arteries involves enhanced production of reactive oxygen species (ROS) and cyclooxygenase activity (COX) and is mediated by 20-hydroxyicosatetraenoic acid (20-HETE) via thromboxane A\(_2\)/prostaglandin H\(_2\) (TP) receptors (thromboxane A\(_2\)/prostaglandin H\(_2\) receptors and attenuated by scavenging ROS); and (3) simultaneous pressure- and flow-induced constriction is necessary to provide effective autoregulation of CBF [29].

Several mechanisms appear to match local blood flow for metabolic requirements; pH, adenosine, ATP, NO, and local neural mechanisms all appear to be involved. The study of muscle activation (contraction) is, in some respects, simpler compared with the study of brain activation. In the brain, astrocytes may be central regulators in the neurovascular unit through their perivascular endfeet by using potassium ions, prostaglandins, ATP, and adenosine, which are critical in brain activities [30].

**Cerebrovascular mechanical autoregulation**

It is known that tissue flow in the brain is approximately 50-55 mL/100 g/min. Under physiological conditions, the human brain accounts for approximately 2% of the total body weight. However, it receives approximately 20% of the cardiac output, demands 20% of the oxygen in the body [10], uses 20% of the body’s resting metabolism, and sodium-potassium pumps consume approximately half of that...
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20% to maintain ionic homeostasis, which is mainly disrupted by spreading depolarization (SD) [9].

In a study from Diamond et al., a biophysical model includes dynamic cerebral autoregulation, which modulates the cerebral arteriole compliance to control cerebral blood flow. Pial arteries and veins are assumed to have constant compliance. When the arterial blood pressure reaches the cerebral circulation, it causes an increase in cerebral arteriole pressure (AP) and arteriole blood flow (ABF). If this increase reaches above the physiological threshold, the autoregulation becomes activated (the threshold of autoregulation activation makes arteriole compliance go to a lower limit), then autoregulation acts by decreasing arteriole compliance (AC) and cerebral arteriole volume (AV) but increases arteriole resistance (AR); the increased AR interacts with the higher AP to lower the ABF to a lower limit. A sustained CBF during this modulation is the expected autoregulation [28]. This response normally has a 2-s delay and occurs within 2-10 s. CBF disturbance occurs by an acute change in arterial blood pressure, and the response occurs much sooner than the mean arterial blood pressure restoration can be detected [31].

**Cerebrovascular neurogenic mechanism and endothelial cell-related factors by neurovascular coupling**

An increase in cerebral activity is followed by a quick increase in CBF to the activated brain areas, O$_2$ demand, and glucose consumption. This coupling is mediated by biochemical and electrical interactions with chemical agents among neurons, astrocytes, the endothelium, and smooth muscle cells [10]. Neural and stromal cells are grouped into a functional entity called a neurovascular unit [32, 33]. Astrocytes respond to neuronal activity by increasing the Ca$^{2+}$ concentrations. The activation of Ca$^{2+}$ in astrocyte endfeet is not only an essential step but also reveals a new level of complexity in the astrocyte control of neurovascular coupling; moreover, vasodilative or constrictive agents are released in response to external factors, suggesting that these cells contribute to the control of CBF changes [34-36].

Astrocytes are particularly positioned as an endfoot process of blood vessels to act as signaling moderators between active neurons and local arterioles, while their other processes still interact with local synapses [37, 38]. The distribution of astrocytes makes it easy to detect neuronal activity, regulate arteriolar diameter changes, and enable blood flow to meet the additional demand of supply in the activated brain region; this process is called “neurovascular coupling”, which is a fundamental feature of brain physiology [39, 40].

**Autoregulatory failure**

When blood flow in the brain decreases to 25-30 mL/100 g/min (40% below normal), electroencephalographic (EEG) abnormalities and altered consciousness may occur. When flow is below 20 mL/100 g/min (60% below normal), EEG becomes isoelectric and neurons switch to anaerobic status, accompanied with a consequent increase in lactate and hydrogen ion production [41, 42]. A flow between 10-12 mL/100 g/min makes neurotransmission and sodium-potassium pumps fail, leading to cytotoxic edema. This initiates a cascade of pathophysiological mechanisms recognized as early brain injury. Many of these metabolic changes lead to endothelial dysfunction and can drive autoregulatory failure [10, 43].

Autoregulatory failure can be divided into three phases as follows. (1) Acute phase. It is known that the acute phase has a prognostic value, and it has been described in poor-grade subarachnoid hemorrhage (SAH) patients in the first few days following an event, with subsequent improvement by day 4, although a study of all-grade SAH patients showed that autoregulation was preserved in the first 2-3 days, suggesting that autoregulation is proportional to ictus severity [44]. (2) Subacute phase, which can be a continuum of the acute phase but also develop in patients with an initial intact autoregulation; it involves a delay in restoring the CBF and is commonly recognized as early brain injury [44]. (3) Delayed cerebral ischemia. This phase develops when consecutive events and prolonged periods of ischemia make neuronal restoration irreversible, leading to infarctions contributing to a high fatality and morbidity [45].

**Spreading depolarization**

Spreading depolarization (SD) is a sustained depolarization of neurons that have been found to originate in patients with stroke, subarach-
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Evidence suggests that SD has three main phases. The first phase involves brief hypoperfusion due to an increase in extracellular K⁺ (> 20 mM) and a decrease in Ca²⁺, leading to vasoconstriction. A decrease in Ca²⁺ blocks NO synthesis, thus inhibiting vasodilation during this early phase; the unbalanced vasoconstriction results in a transient hypoperfusion [52]. A second phase, which lasts for approximately 2 min, is the hyperemic phase. Several vasodilator molecules have been implicated in this marked hyperemia, which originates by an increase in a regional cerebral blood flow (rCBF) influx of more than 100% [53] and is driven by the increased metabolic need for oxygen and glucose [54]. However, distal tissue hypoxia may develop due to the fact that the increase in rCBF is not fully reached to match metabolic needs. Next, a neuronal response glutamate-evoked Ca²⁺ influx in post-synaptic neurons activates the production of NO and arachidonic acid metabolites [9], which contribute to arteriolar dilation [55] and propagation of SD [56]. The last phase is the oligemic period during which rCBF decreases to 69-73% of control values in the cortical regions for 1 h after spreading depression, with a decrease in vascular reactivity [30].

It has been demonstrated there is a transient impairment in CBF autoregulation immediately after SD with restoration over 35 min [57] and that SD leads to neurovascular uncoupling for an hour; however, it is likely that the coupling correlation is altered for much longer, since the shown recovery of the cerebral blood volume, signal amplitude, duration, and time to peak after SD at 60 min post-induction is minimal [58]. Although ionic gradients and subsequent water movements into cells normalize within a few minutes after SD, the metabolites recover to normal values 30 min after SD [57]. Thus, experimental models help to detect the dynamic vascular changes that can be observed after SD.

Conclusion

Cerebral autoregulation is a physiological process in which several mechanisms are involved to maintain constant CBF by changing the mean blood pressure. This ability of the brain can be challenged in several pathologies, which can lead to cerebrovascular autoregulatory failure and concomitant neuronal damage. Adaptation and recovery of the physiological state involves the continuing interchange of ions, electrical and biomechanical interactions, as well as preservation of the synaptic interchange to achieve cerebral autoregulation.

Due to the fact that SD drives failure autoregulation, it can lead to delayed cerebral ischemia. Further studies that analyze the association between SD and autoregulation are necessary to find a viable way to maintain autoregulation in a constant physiological state and avoid consequent neuronal loss.

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