

Review Article

Cerebral Autoregulation in Hypertension and Ischemic Stroke: A Mini Review

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Abstract

Aging and chronic hypertension are associated with dysfunction in vascular smooth muscle, endothelial cells, and neurovascular coupling. These dysfunctions induce impaired myogenic response and cerebral autoregulation, which diminish the protection of cerebral arterioles to the cerebral microcirculation from elevated pressure in hypertension. Chronic hypertension promotes cerebral focal ischemia in response to reductions in blood pressure that are often seen in sedentary elderly patients on antihypertensive therapy. Cerebral autoregulatory dysfunction evokes Blood-Brain Barrier (BBB) leakage, allowing the circulating inflammatory factors to infiltrate the brain to activate glia. The impaired cerebral autoregulation-induced inflammatory and ischemic injury could cause neuronal cell death and synaptic dysfunction which promote cognitive deficits. In this brief review, we summarize the pathogenesis and signaling mechanisms of cerebral autoregulation in hypertension and ischemic stroke-induced cognitive deficits, and discuss our new targets including 20-Hydroxyeicosatetraenoic acid (20-HETE), Gamma-Adducin (Add3) and Matrix Metalloproteinase-9 (MMP-9) that may contribute to the altered cerebral vascular function.

Keywords

Adducin; Cerebral Autoregulation; Hypertension; Matrix Metalloproteinase; Stroke; Vascular Dementia; 20-HETE

Abbreviations

BBB : Blood-Brain Barrier
20-HETE : 20-Hydroxyeicosatetraenoic Acid
Add3 : Gamma-Adducin

MMP-9 : Matrix Metalloproteinase-9
CBF : Cerebral Blood Flow
VSMCs : Vascular Smooth Muscle Cells
CPP : Cerebral Perfusion Pressure
NO : Nitric Oxide
EETs : Epoxyeicosatrienoic Acids
VGCC : Voltage-Gated Calcium Channels
TRPM4 : Transient Receptor Potential Channel of Melastatin Subfamily Four
TRPC6 : Transient Receptor Potential Canonical Subfamily Six
PKC : Protein Kinase C
CO : Carbon Monoxide
H⁺ : Hydrogen Ion
K⁺ : Potassium Ion
KATP : Adenosine Triphosphate Potassium
ATP : Adenosine Triphosphate Channel
MCAO : Middle Cerebral Artery Occlusion
NOS : Nitric Oxide Synthase
A2R : Adenosine 2A Receptor
VCI : Vascular Cognitive Impairment
VaD : Vascular Dementia
AD : Alzheimer's Disease

BP	:	Blood Pressure
AA	:	Arachidonic Acid
ROS	:	Reactive Oxygen Species
NF-kB	:	Nuclear Factor kappa-B
ICAM-1	:	Intercellular Adhesion Molecule 1
VCAM-1	:	Vascular Cell Adhesion Protein 1
SS	:	Salt Sensitive
CNS	:	Central Nervous System
SAH	:	Subarachnoid Hemorrhage
FHH	:	Fawn-Hooded Hypertensive
MMP	:	Matrix Metalloproteinase
KO	:	Knockout

Introduction

Approximately 795,000 strokes occur in the US each year, and there are many survivors [1]. Most of the survivors suffer from neurological damage resulting in significant limitations of daily life. The annual cost to treat stroke survivors is approximately 40 billion dollars in the US and is projected to rise [2]. Approximately 87% of strokes are ischemic [3]. Risk factors for ischemic stroke include aging, hypertension, diabetes, obesity especially with increased waist-to-hip ratio, dyslipidemia, smoking, chronic kidney disease, and other cardiovascular diseases [4]. The mechanisms that link aging, hypertension, stroke and cognitive impairments are not fully understood. There is an urgent need to understand the pathogenesis and discover novel drug targets for prevention and treatment of these devastating diseases. In this brief review, we aim to explore the cerebral autoregulatory signal mechanism and its pathogenesis in hypertension and ischemic stroke-induced cognitive deficits. We discuss new targets including 20-Hydroxy-eicosatetraenoic acid(20-HETE), Gamma-Adducin(Add3) and Matrix Metalloproteinase-9 (MMP-9) that may contribute to the regulation of cerebral vascular function

Materials and Methods

A systemic review of the current literature was performed. We searched MEDLINE, PubMed, Web of Science, and Google through June 2017 using keywords “Cerebral autoregulation, Stroke, Hypertension, Vascular Dementia, 20-HETE, adducin, Matrix Metalloproteinase”. All literature in English was reviewed excluding case-reports, and commentaries. References of included articles were further explored.

Discussion

Autoregulation of cerebral blood flow

Cerebral Autoregulation was first studied by NA Lassen in

1959 [5]. Thereafter the definition has been broadly utilized in explaining global perfusion changes or local circulatory changes [5,6]. Autoregulation of Cerebral Blood Flow (CBF) is a critical homeostatic mechanism that protects the brain from elevations in capillary hydrostatic pressure, vascular damage and cerebral edema following elevations in systemic pressure and from ischemic injury in response to embolization or hypotension [7]. It is generally accepted that autoregulation of CBF is mediated by an interplay between the myogenic response in Vascular Smooth Muscle Cells (VSMCs) acting in concert with the release of vasodilatory metabolic mediators from the surrounding hypoxic brain tissue when Cerebral Perfusion Pressure (CPP) is reduced [8,9]. In response to elevations of transmural pressure in the brain, half of the pressure drop across the cerebral circulation occurs in large arteries [7,10-12], which attenuate 75% of increases in CPP from reaching small pial arteries, and the small pial arterioles and penetrating arterioles account for the remainder of the autoregulation of CBF and capillary pressure [7,13]. On the other hand, in response to the reduction in CPP, the large cerebral arteries dilate as part of the initial cerebral autoregulation. Next, pial and penetrating arterioles, then small pial arterioles dilate following modest to severe reductions in systemic pressure [13,14], and this is mediated by the release of metabolic dilators from the surrounding hypoxic brain tissue including Nitric Oxide (NO), adenosine, prostaglandins and Epoxyeicosatrienoic acids (EETs) [15-17].

Regulating factors and signaling mechanisms of cerebral autoregulation

Myogenic response: The pressure-dependent myogenic response of cerebral vasculature is an intrinsic property of VSMCs since it can readily be demonstrated in de-endothelialized cerebral arterioles *in vitro* [18]. The myogenic response involves depolarization of VSMCs and calcium influx through L-type Voltage-Gated Calcium Channels (VGCC), Ca⁺⁺/calmodulin-dependent phosphorylation, activation of myosin light chain kinase and actin-myosin based contraction [19,20]. There is evidence that Mechanotransduction involves an interaction of cell surface integrins with extracellular matrix proteins. Indeed, blockade of integrins inhibits calcium currents in VSMCs and myogenic tone of skeletal muscle arterioles [21,22]. Recent studies have suggested that the initiation of the myogenic response probably involves activation of nonselective stretch-activated cation channels, such as Transient Receptor Potential Channel of Melastatin Subfamily Four (TRPM4), and Transient Receptor Potential Canonical Subfamily Six (TRPC6) channels via Protein Kinase C (PKC) dependent pathway that depolarizes VSMCs past the threshold for activation of VGCCs [20,23-28]. In addition, activation of Stretch Activated Channels (SOC) and local changes in intracellular Ca⁺⁺ activates the large conductance calcium-activated potassium (BK) channels [19,20], that hyperpolarize VSMCs which inactivates the L-type VGCCs and limits the myogenic response.

Metabolic mechanisms: Cerebral autoregulation is influenced by the release of vasodilatory mediators from the endothelium and surrounding parenchymal tissue in response to the reduction of CPP. These mediators include NO, Carbon Monoxide (CO), prostaglandins, prostacyclin, EETs, adenosine, Hydrogen ion (H⁺), and Potassium ion (K⁺) and Adenosine Triphosphate (ATP). The

release of these compounds is determined by the balance between the steady state energy metabolism, dynamic fluctuations in neuronal activity, arterial PCO₂ and arterial O₂ content. In this regard, release of adenosine [29-31], activation of Potassium Adenosine Triphosphate Channel (KATP) channels [32-35] and release of glutamate leading to increased production of NO have all been reported to contribute to the dilation of pial arterioles associated with hypoxia and ischemia of cerebral tissue following Middle Cerebral Artery Occlusion (MCAO) [33]. However, most of these mediators do not contribute to the metabolic component of autoregulation following CPP reduction within the autoregulatory range in which the tissue is not ischemic. Similarly, blockade of Nitric Oxide Synthase (NOS) and prostaglandins have little or no effect [36-40] on CBF following reductions in CPP in the autoregulatory range. Whereas, reductions in CPP within the autoregulatory range does increase tissue adenosine levels [41] and blockade of Adenosine Deaminase or Adenosine 2A Receptor (A2R) receptors attenuates the vasodilatory response of pial arterioles [39,42]. These results indicate that tissue hypoxia is not required for the release of adenosine. Indeed, adenosine is generated by ecto-nucleotidase enzymatic breakdown of ATP released by neurons and astrocytes [43]. Thus, perivascular generation of adenosine appears to be one of the best candidates that contribute to “metabolic” vasodilation following decreases in CPP.

Hypertension, ischemic stroke and cerebral autoregulation

Hypertension is one of the leading causes of morbidity and mortality regardless of the type of stroke [44]. Cerebral autoregulation is often impaired in hypertensive and aging individuals and contributes to the development of stroke, Vascular Cognitive Impairment (VCI) and Vascular Dementia (VaD) [45-47]. Loss of cerebral autoregulation should increase transmission of pressure to cerebral capillaries resulting in BBB leakage, cerebral edema, inflammation, and neuron degeneration that are commonly seen in patients with VCI [6,46-49]. Chronic hypertension also promotes capillary rarefaction, especially in the deep hemispheric white matter and basal ganglia [46,50]. It is associated with infiltration of perivascular macrophages, increased oxidative stress, endothelial dysfunction, and compromised functional hyperemia [48,51]. These changes promote the formation of small lacunar infarcts, white matter hyperintensities, microinfarcts, and microbleeds, all of which are correlated with a decline in cognitive function in patients with VaD and Alzheimer’s Dementia (AD) [52,53].

Trials in ischemic stroke have demonstrated that both high and lower systolic blood pressure is associated with poor outcomes [54]. The blood pressure plot vs outcomes of ischemic stroke in two different studies demonstrated a ‘U shape’ curve, and a better outcome only exhibited within a very narrow range of Blood Pressure (BP) between 150 mm Hg [54] and 180 mm Hg recorded at the time of the first encounter in emergency [55]. These results along with other studies suggest that increased sympathetic drive is necessary during and immediately after acute stroke attack to maintain a normal cerebral autoregulation for the maintenance of adequate tissue perfusion and expect a better outcome of stroke [54,56,57]. This hypothesis has been confirmed in many

experiments that rapid drop in BP may result in extended infarction due to perilesional ischemia [55,58,59] and increased risk of hemorrhagic transformation [60] in stroke patients with preexhibited cerebral autoregulatory dysfunction, which later results in the pathogenesis of cognitive deficits including vascular dementia [61].

Genes contributing to cerebral autoregulation

Many factors including the role of endothelial dysfunction and hyperemia have been implicated in the regulation of cerebral autoregulation [18,19]. Recent studies have also revealed that several genes may be involved in the myogenic response of cerebral arteries and autoregulation of CBF that may contribute to the pathogenesis of ischemic stroke and cognitive impairment in hypertension and aging. In this review, we focus on the role of 20-HETE, adducin and MMP.

Cytochrome P450 (CYP) 4A and 4F: Enzymes of CYP4A and CYP4F catalyze Arachidonic Acid (AA) to produce 20-HETE. In the Central Nervous System (CNS), 20-HETE is produced primarily in the VSMCs, neurons, and astrocytes [62-64]. It is a potent vasoconstrictor that potentiates the response to angiotensin II and endothelin and ATP, as well as vascular hypertrophy, endothelial dysfunction, angiogenesis, inflammation, apoptosis and platelet aggregation [18-20]. Plasma level of 20-HETE level in plasma increases after acute ischemic stroke [65]. A higher level of 20-HETE promotes inflammation by the production of Reactive Oxygen Species (ROS) and Nuclear Factor kappa-B (NF-κB) in the cerebral vasculature [66]. It also increases cytokines production and expression of adhesion molecules Intercellular Adhesion Molecule 1 (ICAM-1) and Vascular Cell Adhesion Protein 1 (VCAM-1) on B-lymphocytes [67,68] and endothelial cells [69,70] which further promotes margination of macrophages and enhancing inflammatory cascade. Functional genetic variants in CYP4F2 and CYP4A11 that decrease the formation of 20-HETE are linked to hypertension [71,72] and stroke [19,20,73]. Results from animal studies are consistent with these findings in patients. The formation of 20-HETE is reduced in the cerebral vasculature of Dahl Salt Sensitive (SS) rats, and these rats exhibit impaired myogenic response of cerebral arteries and autoregulation of CBF, as well as an increase of BBB leakage in response to elevations in cerebral perfusion pressure [74]. Transfer of wild type CYP4A genes in a chromosome 5 consomic strain or introduction of a wild type of CYP4A1 gene in a transgenic SS strain, restores the production of 20-HETE, autoregulation of CBF and rescues BBB leakage [74]. Recent epidemiological studies have shown associations between genetic variants in the genes that produce 20 HETE with stroke [73], and cognitive impairment [75]. Furthermore, 20-HETE is associated with unfavorable outcome in Subarachnoid Hemorrhage (SAH) patient, likely from acute and delayed cerebral vasospasm after (SAH) [76].

Adducin: Adducin is a cytoskeletal protein that comprises of heterodimers of Alpha-adducin (Add1) with either Beta-adducin (Add2) or Gamma-adducin (Add3). It plays roles in the organization of cytoskeletal structure, cell to cell contact and cell migration and signal transduction [77]. The heterodimers of Add1 and Add3 protein promotes actin-spectrininterac-

tions and regulates actin polymerization [77,78]. Functional variants of Add1 have been linked to the development of hypertension in Milan hypertensive rats and humans [79] by altering the localization of plasma membrane and activity of Na⁺/K⁺-ATPase [80]. More recently, our lab has identified a genetic variant of Add3 in Fawn Hooded Hypertensive (FHH) rats that are associated with impaired myogenic response and autoregulation of renal and cerebral blood flow [81-83]. In addition, knockdown of Add3 expression in both renal and cerebral arteries in normal rats diminishes their myogenic responses *ex vivo* and enhances BK channels activity [78]. Moreover, our recent preliminary work indicated that downregulation of Add3 in FHH rats is associated with an elevation in transmission pressure in the terminal of arteries and the susceptibility of cognitive impairments following the development of hypertension with age [84].

Matrix metalloproteinases: The Matrix Metalloproteinase (MMP) family of zinc-binding proteolytic enzymes degrade collagen and fibronectin [85]. They regulate neutrophil migration across the basement membrane and play an important role in angiogenesis and extracellular matrix remodeling associated with various physiological or pathological processes [86,87]. MMPs are known to play a role in the pathogenesis of atherosclerosis, coronary artery disease and cerebral vascular injury [88,89]. The expression of MMP-2 and MMP-9 are increased in neurons, astrocytes, and microglia [90] following ischemic stroke and intracerebral hemorrhage. Inhibition of MMP-9 reduces infarct size in ischemic stroke rat models [91,92]. MMP9 polymorphisms have been reported to significantly increase the risk of ischemic stroke in Type 2 diabetes [93], and are associated with detrimental functional outcomes in altering the severity of infarct size after the onset of ischemic stroke [89,94]. Moreover, thrombolysis (t-PA) has been reported to enhance MMP-9 release which further enhances neuronal damage resulting in edema and hemorrhagic transformation [95]. MMP9 is associated with mild cognitive impairment and VCI [96-98]. Whereas, treatment with human cord plasma containing MMP-2 inhibitor restores the hippocampal function and improves cognition in aged mice [99].

The role of MMPs in hypertension and ischemic stroke-induced cognitive deficits is multifactorial. Mechanistically, MMPs activate migration and proliferation of VSMCs [85,89], and facilitate inflammation and perivascular fibrosis [100]. Whether they regulate cerebral autoregulation has not been elucidated. Elevated levels of MMP-9 have been found in SS rats, inhibition of MMP-9 reduces oxidative stress and endothelial dysfunction and attenuates cerebrovascular dysfunction in this strain after the development of hypertension [101]. Knockout (KO) of MMP-9 protects against ischemic and traumatic brain injury in mice and is mediated by reduced BBB leakage and white matter damage [85]. Results from our recent studies in MMP-9 KO SS rats are consistent with these findings. Furthermore, we found that the impaired myogenic response and autoregulation of CBF in hypertensive SS rats are restored in the MMP-9 KO strain [102]. Inhibition of MMP-9 now is examined as a therapeutic strategy in ischemic stroke [103].

Conclusion

Cerebral vascular dysfunction is a rising concern that contributes

to cognitive impairments, including Alzheimer's disease and vascular dementia. Hypertension and ischemic stroke-induced cognitive deficits are often associated with impaired myogenic response and autoregulation of CBF. Genetic variants in genes involved in regulation of cerebrovascular function are linked to hypertension, stroke, and dementia. Understanding the vascular pathogenesis may help to explore novel drug targets to delay the onset and prevent the progression and severity of these currently incurable diseases.

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