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REVIEW ARTICLE

Involvement of endothelial-derived relaxing factors in the regulation of cerebral blood flow

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Abstract Despite numerous researches and advances in the present times, delayed cerebral vasospasm remains a severe complication leading to a high mortality and morbidity in patients with subarachnoid hemorrhage (SAH). Since the discovery of endothelium-derived relaxing factor (EDRF) in 1980, its role in delayed cerebral vasospasm after SAH has been widely investigated as well as in regulation of basic cerebral blood flow, pathophysiology of vasoconstriction and application on prevention and treatment of cerebral vasospasm. Among all the EDRFs, nitric oxide has caught the most attention, and the other substances which display similar properties with characteristics of EDRF such as carbon monoxide (CO), hydrogen sulfide (H_2S), hydrogen peroxide (H_2O_2), potassium ion (K^+) and methane (CH_4) have also evoked great interest in the research field. This review provides an overview of recent advances in investigations on the involvement of EDRFs in the regulation of cerebral blood flow, especially in cerebral vasospasm after SAH. Possible therapeutic measures and potential clinical implications for cerebral vasospasm are also summarized.

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Introduction

The endothelium-derived relaxing factor (EDRF) was discovered by Furchgott and Zawadzki [1] in 1980 by finding that acetylcholine (Ach) evoked vasodilation only when the endothelial cell layer of the vascular strip was kept intact, while it caused vasoconstriction when the endothelium was removed. They resolved the long-standing discrepancy that Ach-induced vasodilation when administered in vivo, but vasoconstriction in isolated vascular strips. The release of a factor from endothelial cells induced by acetylcholine was proposed, which transferred to the vascular smooth muscle cells (VSMCs) and caused vasodilation by relaxing VSMCs [2].

Nitric oxide (NO), first identified as EDRF by Palmer et al. in 1987 [3] and the most well-known EDRF [4], is produced by endothelial nitric oxide synthase (eNOS) in the intima and by neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) in the adventitia of cerebral vessels and smooth muscle cells [5–7]. Other substances which display properties in common with the characteristics of EDRF include carbon monoxide (CO) [8, 9], hydrogen sulfide (H_2S) [10, 11], hydrogen peroxide (H_2O_2) [12], potassium ion (K^+) [13, 14] and methane (CH_4) [15].

Delayed cerebral vasospasm after subarachnoid hemorrhage accounts for permanent neurological deficits or death owing to delayed ischemic neurological deficits (DIND) in

at least 15% of patients following otherwise successful treatment for intracranial aneurysm rupture [16]. The role of NO in cerebral vasospasm after SAH has evoked much interest because of its higher affinity for hemoglobin than oxygen [17] and its vasodilating effects in the regulation of cerebral blood flow [18, 19].

Extensive literature has been produced after the discovery of EDRF and contains numerous reports about the role of EDRFs in cardiovascular function and pathophysiology in the brain. This review provides an overview of recent advances in these investigations, mainly focusing on the involvement of EDRFs in the regulation of cerebral blood flow, especially in cerebral vasospasm after SAH. Potential therapeutic measures and potential clinical implications for cerebral vasospasm are also summarized.

Involvement of NO in pathophysiology, prevention and reversal of delayed cerebral vasospasm

NO is a free radical gaseous molecule formed by constitutive isomers of NO synthase, endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) from the substrate L-arginine in endothelial cells, autonomic nitrergic nerves or brain neurons under resting and simulated conditions; while overproduction of NO participates in pathological conditions resulting from nNOS induction and iNOS activation [4]. It is rapidly inactivated to nitrite or nitrate by oxidation. NO can directly activate soluble guanyl cyclase (sGC) to catalyze the conversion of GTP to cyclic GMP in smooth muscle cells [20]. Increased levels of cyclic GMP lead to prevention of Ca^{2+}-dependent activation of myosin light-chain kinase and muscle contraction by reducing intracellular free Ca^{2+} concentration or Ca^{2+} sensitivity [21, 22]. Cyclic GMP-independent mechanisms, such as S-glutathiolation or oxidation of sarco/endoplasmic reticulum Ca^{2+} ATPase [23], activation of Ca^{2+}-dependent K^+ channels [24] and activation of ATP-sensitive K^+ channel [25], have been suggested to be involved in NO-induced vascular smooth muscle relaxation. In addition to causing vasodilation, decreasing vascular resistance and lowering blood pressure, NO derived from endothelial cells can also inhibit platelet aggregation and adhesion, inhibit leukocyte adhesion and migration, and reduce smooth muscle proliferation [18]. On the basis of numerous studies, it has been suggested that NO release plays a crucial role in the regulation of cerebral blood flow (CBF) [18], including basal release under resting conditions [26] and stimulated or suppressed release under pathophysiological or interventional conditions. Moreover, NO production can also be mediated by tissue plasminogen activator (tPA), dependent or independent of *N*-methyl-D-aspartate (NMDA) receptors activation, low-density lipoprotein receptor-related protein or annexin II [27, 28]. Thus, tPA has a role in vital homeostatic mechanisms by modulating nitric oxide synthase and in local cerebral perfusion.

In animals subjected to SAH, oxyhemoglobin (oxyHb) gradually released from blood clots in the subarachnoid space via erythrocyte lysis is a powerful scavenger of NO [29] and destroys nNOS-containing neurons in the conductive arteries. The function of eNOS, which is stimulated by increased shear stress because of artery narrowing [30], is also impaired due to increased activity of phosphodiesterase (PDE) leading to quicker elimination of 3′, 5′-cGMP [31], or endogenous inhibition by asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of NOS [32], in response to the existence of bilirubin-oxidized fragments (BOXes) in hemorrhagic cerebrospinal fluid (CSF) [33, 34]. Together with vasoconstricting factors such as endothelin-1 (ET-1), cyclooxygenase (COX) products, reactive oxygen species (ROS), etc. [35], the decreased bioavailability of NO derived from endothelium, neurons and nitrergic nerve would lead to cerebral vasospasm after SAH. Excessive production of NO after induction of iNOS expression also plays a role under pathological conditions such as inflammation and cerebral ischemia, leading to generation of peroxynitrite and other highly toxic compounds by reacting with superoxide anions. This may account partly for the delayed ischemic neurological deficit after subarachnoid hemorrhage. Also, previous studies have demonstrated that iNOS inhibition might yield therapeutic methods to alleviate ischemic brain injury [36]. On the other hand, preconditioning mediated by eNOS might have beneficial effects on reducing vasospasm and cerebral ischemia after SAH [37]. Thus, according to these observations, the key therapeutic target in cerebral vasospasm after SAH would be exogenous administration of NO donors, inhibition of PDE and BOXes, and prevention of oxyHb neurotoxicity [19, 38].

The effectiveness of L-arginine on cerebral vasospasm after SAH displays discrepancy [39–41] probably due to differences of animal species, route of drug administration or dosage. In animal models, intravenous administration of nitroglycerin (NTG) or sodium nitroprusside (SNAP) with NO in the form of nitrates could prevent cerebral vasospasm effectively [41, 42]. However, it is limited for its strong hypotensive effect [41, 43], which may evoke the risk of potential ischemic complications especially in hemodynamically unstable patients with cerebral vasospasm after SAH. Low-dose NTG delivery via a transdermal patch effectively prevented cerebral vasospasm in a rabbit model of SAH without significant changes in blood pressure and may provide a possible treatment for cerebral vasospasm [42], but its effectiveness needs to be evaluated clinically. Nitrite, which is reported as an endogenous NO

donor in blood [44], may provide a way to overcome reduced NO production in the arterial wall after SAH by intravenous administration [38]. In a primate SAH model, intravenous continuous delivery of sodium nitrite for 14 days prevents development of vasospasm without changes on blood pressure demonstrating that nitrite could release NO locally in the subarachnoid space [45]. However, further study on nitrite needs to be done to elucidate pharmacokinetics of sodium nitrite in humans and establish proper dosage and safety profile. Regional (intracarotid/intracerebral arterial) or local (intrathecally or intraventricular) delivery of NO donors are limited for use and not clinically attractive because of increased risk of severe complications or surgical access [38]. Inhibition of ADMA production or PDE may also be able to alleviate vasospasm by restoring NOS or cGMP, but experimental and clinical studies need to be carried out [38].

In short, NO has been proved to display protective and destructive duality depending on the pathophysiological conditions and different isoforms of NOS. It plays an important role in occurrence, development and treatment of cerebral vasospasm and delayed ischemic neurological deficit after SAH. This points to the administration of NO donors as a direction on prevention and reversal of vasospasm, and nitrite seems to be an ideal donor candidate. However, both basic and clinical studies need to be done to elucidate the timing, dosage, route of delivery and possible side effects in patients with unstable hemodynamics after subarachnoid hemorrhage.

Involvement of CO in induction of vasorelaxation

CO is known for being poisonous at high concentrations. It attaches to hemoglobin (Hb), forming carboxyhemoglobin (COHb) and thus inhibiting oxygen delivery to organs and tissues, inducing delayed development of central nervous system impairment and neurobehavioral consequences [46]. However, CO could be endogenously produced as by-products via the metabolism of heme in which heme oxygenase (HO) catalyzes the degradation of heme to biliverdin, iron and CO [47]. HO has two distinct isoforms, inducible isozyme HO-1 and constitutive isozyme HO-2, both of which can be found in arterial smooth muscles and endothelial cells [48, 49]. It is suggested that endogenously generated CO-induced vasorelaxation is induced by activating Ca^{2+} -activated K^+ channel (K_{Ca}) and cGMP signaling pathway in VSMCs [50, 51], both of which are also activated in vasorelaxation of cerebral arteries by CO [52]. There is also evidence implicating that CO augments K_{Ca} channel activation by increasing the effective coupling of intracellular Ca^{2+} transients (Ca^{2+} sparks) to K_{Ca} channels in arterial smooth muscle cells [53]. Cerebral dilator effects of CO could also be mediated by NO depending on animal species [18, 54]. A previous study suggested that afferent arteriole autoregulatory responses to increases in renal perfusion pressure is modulated by an augmented HO system in pathophysiological condition via CO production [55], which implies there might be a similar condition in cerebral autoregulation to be investigated.

According to the above observations, CO is implied to have a potential role in cerebral blood flow regulation in both resting and pathophysiological states. It also might be involved in cerebral vasospasm after SAH [8]. CO generated by induction of HO-1 in cerebral arteries in a primate SAH model [56] and in glia and whole brain in rats SAH models [57, 58] may provide a limited effect on vasodilation, but an important role in protection against oxidative injury. Still, for the limited study on CO and cerebral vasospasm after SAH, there remain numerous studies that explore the role of CO in the occurrence of vasospasm, mechanisms involved in cerebral blood flow regulation and new therapeutic approaches of vasospasm based on the HO system and CO without neurotoxicity and other side effects. The interaction between CO and NO also needs to be investigated [47].

Involvement of H_2S in vascular relaxation

H_2S, known as a poisonous and toxic gas of the rotten egg, is endogenously produced from the metabolism of L-cysteine by constitutively expressed enzymes, including cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE) that is predominantly expressed in the endothelial layer of blood vessels [59, 60]. H_2S produced by CSE can enhance outward flux of K^+ via opening K^+ channels, resulting in hyperpolarization of membrane potential and vascular smooth muscle relaxation [61–63]. The vascular effects of H_2S are suggested to be partially mediated by a functional endothelium and depend on the extracellular calcium entry without the activation of cGMP signaling pathway [64]. A study by Yang et al. [10] showed that CSE gene knockout mice display significant hypertension and decreased endothelium-dependent vasorelaxation, with profound reduction of H_2S levels in serum, heart, aorta and other tissues. Intravenous delivery of NaHS, which is an H_2S donor, can transiently decrease systolic blood pressure of these mice, suggesting that H_2S has the effects of physiologic vasodilation and regulation of blood pressure. It is also suggested to regulate smooth muscle tone in coordination with NO [65].

The important role of H_2S in regulating vascular smooth muscle tone and blood pressure imply a possibility of its involvement in regulation of cerebral blood flow, cerebral vasospasm after subarachnoid hemorrhage and its potential

therapeutic effect in prevention and reversal of vasospasm. Since the study on H_2S associated with cerebral vasospasm after SAH is quite limited, more work should be performed from the basic study.

Involvement of H_2O_2 in vascular tone regulation

As a chemically relatively stable reactive oxygen species (ROS), H_2O_2 can be endogenously generated by oxidative enzymes such as xanthine oxidase directly or produced by spontaneous or catalyzed dismutation of superoxide. It induces the relaxation of cerebral arteries [66] by activating Ca^{2+}-activated K^+ channels in vascular smooth muscle cells [67–69] and a nonselective cation channel in the endothelium [70]. A pre-existing study performed by Capettini et al. [12] showed that catalase could reduce Ach-induced vascular relaxation and abolish Ach-induced H_2O_2 production by degrading H_2O_2. Also, antisense knockdown of eNOS does not diminish H_2O_2 production, but decreases Ach-induced relaxation, suggesting that nNOS-derived H_2O_2 is an important endothelium-dependent relaxing factor.

According to the reports on H_2O_2 associated with vasodilation of cerebral arteries, it may be partly involved in CBF regulation and pathogenesis of cerebral vasospasm and may be another target for prevention and treatment of cerebral vasospasm.

Involvement of K^+ in cerebral vasospasm

K^+ is suggested to be an endothelium-derived hyperpolarizing factor (EDHF) [13] derived from endothelial cells and could relax arterial smooth muscle mediated by Na^+–K^+ ATPase and inward rectifier K^+ channels (K_{IR}) [14, 71]. VSMCs are reported to be depolarized during vasospasm after subarachnoid hemorrhage [72], and conversely their hyperpolarization induced by opening of K^+ channels will close voltage-gated Ca^{2+} channels, reduce intracellular Ca^{2+} and lead to vascular relaxation [71]. In a rabbit SAH model of cerebral vasospasm, systemic delivery of cromakalim, an activator of ATP-sensitive K^+ (K_{ATP}) channels, could prevent and attenuate delayed cerebral vasospasm [73, 74]. Locally, intrathecal delivery of cromakalim could prevent cerebral vasospasm in a rat SAH model as well [75]. Expression of K_{IR} increased during vasospasm after SAH, and blockage of K_{IR} would aggravate artery contraction in a dog SAH model, suggesting the increase of K_{IR} as a compensatory mechanism to reduce vasospasm [71]. Voltage-gated K^+ channels (K_v), but not K_{Ca} channels [76, 77], may contribute to the pathogenesis of cerebral vasospasm after SAH. K^+ is also involved in vasoactive effect of NO, CO, H_2S and H_2O_2 as discussed above. An in vitro study previously also proposes that an R-type voltage-dependent Ca^{2+} channel (VDCC) induced by oxyhemoglobin may contribute to enhanced cerebral artery constriction after SAH [78, 79].

According to current reports, certain K^+ channel openers may provide a possible method for prevention and treatment of cerebral vasospasm after subarachnoid hemorrhage, but more experimental and clinical studies need to be carried out to determine the route of delivery, dosage, frequency and time duration due to the risky or even lethal effects of high K^+ concentration in blood. Additionally, specific VDCC blockers may provide a means for the therapy of cerebral vasospasm without causing systemic hypotension [79].

Possible involvement of CH_4 in endothelium protection and ischemia

Methane, previously regarded to be exclusively produced by bacteria from decomposing organic matter in the gastrointestinal tract of mammals [80, 81], has been found to form in both rat liver mitochondria and bovine aortic endothelial cells [15, 82]. It is generated in greater amounts in bovine endothelial cells under hypoxic conditions in an in vitro study [82]. CH_4 plasma coating on intraocular lenses is proved to protect endothelial cells from damage, mostly attributing to its hydrophilic effects, while other possible mechanisms involved are not clear yet [83]. These studies imply a possibility that CH_4 may have a role in endothelium protection following cerebral ischemia with low oxygen delivery accompanying cerebral vasospasm, and indirectly preserve the production of the other EDRFs. However, its involvement in vascular tone regulation and SAH has not been investigated. Further study requires to be conducted on the possible vasoactive effects of methane due to its endothelium-protective role, whether and how SAH affects the production and function of methane, and prospectively prophylactic and therapeutic methods taking methane as a target.

Summary

The pathophysiology of cerebral vasospasm after subarachnoid hemorrhage is complicated and needs to be further clarified. The role of NO in the regulation of cerebral blood flow, pathogenesis and treatment of cerebral vasospasm and delayed ischemic neurological deficit after SAH is mostly investigated. Studies on other EDRFs associated with cerebral vasospasm are limited and may provide potential targets for possible development of

preventive and therapeutic measures on regulation of cerebral blood flow and cerebral vasospasm after SAH. Interaction among these factors and other vasoactive factors are also to be investigated. The inflammatory response accompanying SAH may represent a crucial pathway in the pathogenesis of cerebral vasospasm and delayed ischemic neurological deficit [84, 85], which is not discussed in this article. Howwever, these EDRFs may have some other involvements in this pathway with anti- or proinflammatory effects. Experimental and clinical research is required to elucidate the role of EDRFs in regulation of cerebral blood flow and cerebral vasospasm, the interventional methods for prevention and reversal of vasospasm, and protection from neurological ischemic deficits.

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