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Review

Oxidative stress as a bridge between age and stroke: A narrative review

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ABSTRACT

Stroke is the third most common cause of death globally and a leading cause of disability. The cellular and molecular changes following stroke and causes of neuronal death are not fully understood, and there are few effective treatments currently available. A rapid increase in the levels of reactive oxygen species (ROS) post stroke can overwhelm antioxidant defenses and trigger a series of pathophysiologic events including the inflammatory response, blood-brain barrier (BBB) disruption, apoptosis, and autophagy, ultimately leading to neuron degeneration and apoptosis. It is thought that beyond a certain age, the ROS accumulation resulting from stroke increases the risk of morbidity and mortality. In the present review, we summarize the role of oxidative stress (OS) as a link between aging and stroke pathogenesis. We also discuss how antioxidants can play a beneficial role in the prevention and treatment of stroke by eliminating harmful ROS, delaying aging, and alleviating damage to neurons.

Introduction

Stroke is an age-related disease that leads to neurologic dysfunction and is associated with high rates of disability and mortality.[1-3] Stroke can be classified into hemorrhagic stroke (HS) and ischemic stroke (IS), with the latter accounting for 87% of cases. HS is caused by bleeding in or around the brain,[4] whereas IS is caused by disruption of the brain's arterial blood flow by thrombosis, embolism, or cerebrovascular rupture, resulting in ischemic necrosis of brain tissue and loss of neuronal function.[5-7] IS is the third leading cause of death worldwide, with nearly 15 million people affected yearly.[8,9]

Post-stroke patient care involves correctly identifying the type of stroke based on clinical findings. IS patients have higher mean Glasgow Coma Scale scores than HS patients,[10] who frequently experience acute onset headaches. Computed tomography (CT) findings include a mass effect, hypodense lesions, hyperdense artery signs, and sulcus effacement in IS and hyperdense lesions in HS.[11] The prognosis of patients is determined by the type of stroke, degree and length of blockage or bleeding, and severity of neurodegeneration. The location of the lesion is also important in HS, which has a worse outcome than IS.[12] Age adversely affects IS pathophysiology and prognosis.[13-15] Currently, 11% of the world's population is over 60 years old, with the percentage expected to reach 22% by 2050.[16] Clarifying the pathophysiology of age-related IS is critical for developing new treatments.

Few pharmacotherapies are effective in mitigating the effects of stroke.[17-19] Revascularization therapies such as thrombolysis recombinant tissue plasminogen activator and endovascular thrombectomy have been shown to reduce the disability rate of patients with acute cerebral infarction within 24 h.[20,21] However, ischemia-reperfusion injury after revascularization therapy can worsen outcomes.

The pathophysiology of stroke is complex. The acute disruption or reduction of cerebral blood flow and resultant decrease in available oxygen causes focal or global damage to brain tissue, with characteristic biochemical and molecular changes that can lead to transient or permanent neurologic sequelae or death.[22-25] The main products of the oxidative stress (OS) response - i.e., free radicals including reactive oxygen species (ROS) - can damage brain tissue and are an important

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pathologic mechanism of stroke. Antioxidants that remove free radicals can limit neuronal injury following stroke [26-28] and are thus a potential treatment for IS.

Overview of OS and the Antioxidant System

OS occurs when there is an imbalance between oxidation and antioxidation, which leads to neutrophil infiltration, increased protease secretion, and production of oxidative intermediates.[29] Under pathologic conditions such as brain hypoxia, oxygen free radicals accumulate and cause damage to cell membranes, especially that of mitochondria. This lead to neuronal dysfunction and death; thus, interventions that alleviate OS are a potential treatment strategy.[30-32] There are two types of antioxidant system in the body: enzymatic (which includes glutathione peroxidase [GSH-Px], glucose-6-phosphate dehydrogenase [G6PD], catalase [CAT], and superoxide dismutase [SOD]) and non-enzymatic (which includes vitamins and phenols). Their potential roles in stroke are discussed below.

Molecular Mechanisms of Stroke

Excitatory neurotoxicity, oxidative/nitrosative stress, mitochondrial dysfunction, and calcium overload are the main causes of stroke. Cellular damage from free radicals, mainly OS/nitrosative stress injury, plays a critical role in ischemia-reperfusion injury.[33] Under normal conditions, electrons produced by metabolism through the mitochondrial respiratory chain combine with oxygen and are reduced to water. Under hypoxia, an excess of electrons combine with iron and other molecules to produce free radicals.[34] Restoration of blood flow results in a sudden increase in oxygen content, leading to peroxide production via the reaction between electrons and oxygen molecules. Following cerebral ischemia/reperfusion, tissue acidification, cell membrane depolarization, calcium influx, neurotransmitter release, and inflammatory cell infiltration can generate free radicals that are inactivated by antioxidants.[35]

ROS are produced by various cellular structures and molecules including mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH), nitric oxide synthase (NOS), and xanthine oxidase.[36] SOD, CAT, and GSH-Px are present at low levels in the brain and the concentration of free radicals in brain tissue during hypoxia and reperfusion can exceed the antioxidant capacity of these enzymes. The accumulation of ROS can lead to apoptosis, tissue inflammation, DNA damage, lipid peroxidation, and protein degeneration.[37]

Role of Mitochondria in OS

Mitochondrial dysfunction is linked to age-related disorders such as metabolic syndromes, neurodegenerative and cardiovascular diseases, and cancer.[38] Mitochondria regulate energy metabolism and maintain cellular homeostasis. Aging is associated with decreased mitochondrial activity and accumulation of damaged mitochondria in various tissues.[39]

Mitochondrial distribution and activity influence neuron morphogenesis and synaptogenesis, developmental and synaptic plasticity, and axogenesis. Axons and dendrites form synapses after neural stem cells divide and differentiate into neurons over the course of development.[40] Mitochondria participate in neuroplasticity through the formation of adenosine 5′-triphosphate, generation of ROS and reactive nitrogen species (RNS), induction of apoptosis, and maintenance of calcium homeostasis. ROS and RNS interact with mitochondrial proteins, lipids, and DNA, at least in part through their proximity.[41] OS induces the release of proapoptotic mitochondrial proteins into the cytosol through interactions between mitochondrial and extramitochondrial proteins that can be inhibited by other proteins and small molecules.[42]

Changes in mitochondrial dynamics and quality control can lead to mitochondrial damage, which in turn contributes to senescence. Thus, strategies that improve or restore these processes may prevent aging and age-related disorders.[43]

Role of OS in Stroke

OS is a pathologic process resulting from an imbalance between ROS production and removal.[44] Excessive ROS in brain tissue can damage the mitochondrial membrane through lipid peroxidation, leading to destruction of the respiratory chain.[45] ROS in neurons damage mitochondrial DNA, inactivate enzymes and degrade proteins in mitochondria, and destroy cell membrane structure and function, causing neuronal death.[46] They can also affect cerebral blood flow, causing vasodilation and increasing endothelial cell permeability, causing damage to vascular endothelial cells, increasing blood-brain barrier (BBB) permeability, and leading to impairment of brain tissue microcirculation,[47] thereby aggravating the OS response and glutamate excitotoxicity.[48] The associated changes in mitochondrial dynamics can lead to upregulation of N-methyl-D-aspartate receptors and further enhance the OS response and induce neuronal death.[49] These processes can damage brain tissue and contribute to the pathogenesis of stroke (Figure 1).

Relationship Between Aging, OS, and Stroke

OS is associated with aging and is a feature of aging-related vascular diseases including stroke.[50] Aging is itself a risk factor for worse prognosis following stroke.[51-54] However, the molecular links between aging, OS, and stroke are not fully understood.[16] We speculate that age directly exacerbates stroke outcomes by inducing oxidative damage.

Byproducts of normal oxidative metabolism can cause damage to DNA, lipids, and proteins that contribute to aging.[55,56] Superoxide (O_2), hydrogen peroxide (H_2O_2), and hydroxyl radicals are produced upon exposure to mutagens but are also byproducts of normal metabolism.[57,58] Lipid peroxidation produces mutagenic lipid epoxides, lipid hydroperoxides, lipoalkoxy and peroxide radicals, and enaldehydes. Singlet oxygen, a high-energy oxygen molecule, is produced by light-induced energy transfer, respiratory bursts of neutrophils, or lipid peroxidation.[59,60] Despite the activities of physiologic antioxidant defense systems, DNA may sustain oxidative damage [61] that cannot be repaired; meanwhile, other cellular repair systems such as the proteasomal degradation of damaged proteins may also decline with aging.[62] Adaptive responses to OS decrease with aging as a result of telomere dysfunction in cellular senescence and induction of senescence-associated secretory phenotypes (SASP) and dysregulation of metabolism.[63-65]

Increased OS and neuroinflammation in the aging hippocampus is a major cause of age-related cognitive decline and de-

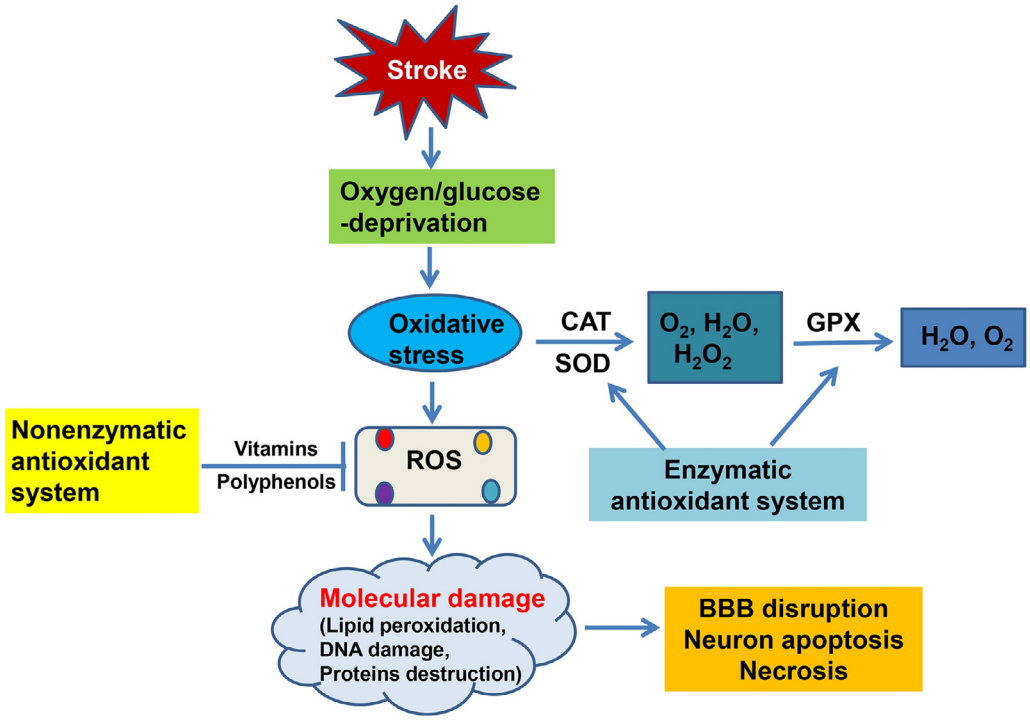

Figure 1. Schematic illustration of oxidative mechanisms, OS-mediated molecular damage, and antioxidant mechanisms in stroke.
BBB: Blood-brain barrier; CAT: Catalase; GSH-PX: Glutathione peroxidase; OS: Oxidative stress; ROS: Reactive oxygen species; SOD: Superoxide dismutase.

creased neurogenesis and synaptic plasticity.[66] Post-ischemic microglia exhibit reduced interaction with neighboring neurons and polarization toward the infarct lesion, which may contribute to aging-associated vulnerability to and poorer recovery from IS.[67] Hallmarks of brain aging include OS, reduced adaptive neuroplasticity and resilience, aberrant neuronal network activity, impairment of DNA damage repair, and dysregulated energy metabolism.[68] Mitochondrial dysfunction under ischemic conditions increases with age and causes the loss of neurovasculature integrity and injury to brain tissue.[55] Aging can also damage collateral circulation and prevent brain revascularization, which is associated with increased endothelial NOS activity and decreased expression of inflammatory response markers, which result in the aggravation of stroke [69,70] (Figure 2).

Antioxidants in Stroke

Relationship between aging, antioxidants, and stroke

The relationship between aging and antioxidants is complex and the rate of aging is thought to be more significant than chronological age in terms of disease risk.[71] Antioxidants, which slow the aging process by reducing or maintaining the levels of oxidizing molecules, can be obtained through the diet and may be included in cosmetic products to counter the skin cell-damaging effects of free radicals. Several biomolecules and compounds with redox activity have been identified that can slow the aging process.[36,72-76] Additionally, as OS is increased in the ischemic brain, antioxidants have been evaluated for their neuroprotective potential in stroke. In animal models, ischemic damage to brain tissue was mitigated by administering BBB-penetrating antioxidant molecules such as polyethylene glycol-conjugated SOD, CAT, and lazaroids; and infarct size was decreased in SOD transgenic mice but increased in SOD knockout mice compared with their wild-type counterparts.[73] A technical challenge when investigating the relationship between OS and stroke is the accurate quantification of free radicals generated in brain tissue.[75] Indirect evidence of OS during ischemia includes elevated levels of lipid peroxidation products and lower levels of antioxidants in tissues.[74] Additionally, it was reported that patients with stroke had lower plasma vitamin C and E levels than non-stroke patients, whereas the levels of thiobarbituric acid-reactive substances were elevated 2 days after the onset of cerebral ischemia.[36,76]

GSH-Px

GSH-Px, a peroxidative CAT, is a powerful radical scavenger that catalyzes the transformation of glutathione to oxidized glutathione, reducing toxic peroxide to nontoxic hydroxyl compounds that promote the breakdown of H_2O_2 into water and oxygen. Thus, GSH-Px can prevent oxidative damage to the cell membrane, thereby preserving cell structure and function.[77,78] Plasma GSH-Px activity was shown to be reduced in patients with acute IS [78] and a decrease in GSH-Px level is an independent risk factor for arterial IS.[79] GSH-Px deficiency increases extracellular OS, reduces bioavailable nitric oxide, and promotes platelet activation. In patients with acute IS, red blood cell GSH-Px activity was significantly reduced within 24 h after the onset of stroke symptoms compared with control patients,[80] and in an animal model, GSH-Px protected against ischemic brain injury whereas a reduction in GSH-Px level was associated with an increased risk of stroke.[81] These findings indicate that GSH-Px can serve as a biomarker for progression of reac-

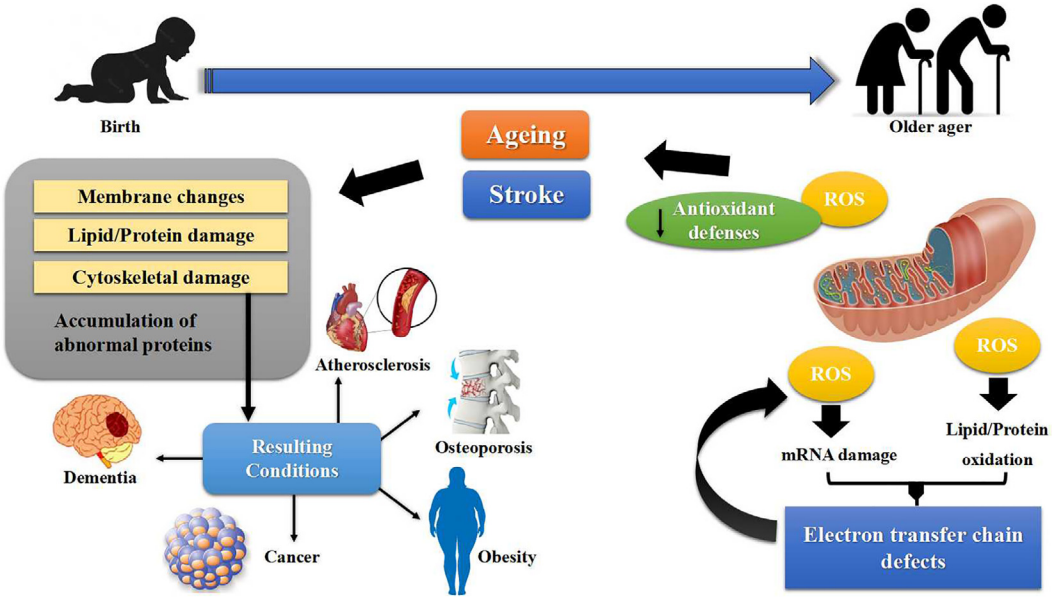

Figure 2. Proposed interactions between age-related diseases and stroke. ROS: Reactive oxygen species.

tive stroke and has clinical value for the differential diagnosis of stroke.

G6PD

G6PD is a rate-limiting enzyme in the pentose phosphate pathway (PPP), which plays an important role in neuronal survival during cerebral ischemia-reperfusion. G6PD deficiency has been linked to the development of stroke and is associated with poor prognosis following IS, increasing the risk of in-hospital mortality.[82] Additionally, stroke patients with G6PD deficiency may have worse safety outcomes with long-term low-dose aspirin therapy.[83] It was also reported that acute stroke patients with G6PD deficiency had a higher risk of poor clinical outcomes with thrombolysis therapy than in patients with normal G6PD levels.[84] Thus, G6PD level may reflect to some degree the extent of brain damage from stroke.

CAT

CAT is an oxygen radical-scavenging enzyme that mainly exists in tissues and erythrocytes. CAT metabolizes H_2O_2 to H_2O and O_2 and removes hydrogen from H_2O_2, causing the reaction of H_2O_2 with O_2 and iron chelators to prevent damage to cell membranes by H_2O_2.[85,86] CAT levels were found to be lower in patients with acute IS than in healthy controls, and a reduction in CAT level exacerbated the cellular response to OS.[87]

SOD

SOD catalyzes the partitioning of superoxide anion free radicals to O_2 and H_2O_2 [88] and is the main enzyme preventing cellular damage from oxygen radicals; its activity reflects the extent of damage involving lipid peroxidation.[89,90] Reduced SOD activity can lead to the accumulation of metabolites that induce oxidative damage.[91] Serum SOD levels in acute-phase IS may serve as a marker of stroke-associated infection; meanwhile, increased SOD levels can protect against brain injury.[92] In an animal model of IS, manganese SOD reduced infarct volume, improved neuronal function, and reduced OS and apoptosis.[93] This evidence suggests that SOD can reduce OS and has therapeutic benefits in preventing IS.

Non-enzymatic antioxidants

Non-enzymatic antioxidants including vitamins and phenols for the treatment of stroke are used in traditional Chinese medicine. Some of these are discussed in the following sections.

Vitamins

Vitamin C is a highly reductive polyhydroxy compound with antioxidant effects.[94] Ascorbate, the biologically active form, is critical for homeostasis and the regulation of neuron function[120]. Brain vitamin C content was shown to be closely related to cognitive decline and stroke severity.[95] An excess of free radicals can lead to lipid peroxidation and IS.[96] Vitamin C prevents atherosclerosis by reducing monocyte adhesion to the endothelium of blood vessels, reducing blood pressure, promoting vasodilation, increasing intravascular nitric oxide, and inhibiting low-density lipoprotein (LDL) peroxidation to reduce the risk of IS. Ascorbate was shown to protect neurons from glutamate excitotoxicity by modulating glutamate receptor activity and lowering the level of free radicals produced by glutamate release. High doses of vitamin C may decrease the severity of ischemia [97] and alleviate cognitive impairment in a rat model of sepsis via a protective mechanism involving suppression of inflammation and OS and modulation of heme oxygenase 1 (HO-1) signaling.[98] However, whether vitamin C can improve the outcome of patients with IS remains to be investigated in large-scale randomized controlled clinical trials.

Polyphenols

Phenolic compounds exert antioxidant effects through multiple mechanisms; these include downregulating key enzymes involved in ROS formation, combining with metal ions, and

enhancing ROS clearance.[46,99] They may also protect plasma membrane structure and function by altering its properties to prevent the entry of oxidant molecules. Flavonoid polyphenolic compounds may inhibit peroxidase activity and neutrophil release.[100] Phenolic compounds regulate nitric oxide production by interacting with NOS, thereby reducing oxidative damage in cardiovascular disease.[101] In atherosclerosis, polyphenolic compounds inhibit LDL peroxidation to prevent IS,[102] and they also play an important role in preventing IS by protecting neurons from the OS response through inhibition of lipid peroxidation [103] (Figure 1).

Free radical products

Malondialdehyde (MDA) is the end product of fatty acid peroxidation under OS and indirectly reflects neuronal damage caused by free radicals.[104] Elevated plasma MDA levels have been reported in stroke patients.[105] Elevated plasma lipid H_2O_2 level in stroke patients at admission was shown to be correlated with the severity of neurologic defects.[106] Thus, MDA level is an indicator of stroke severity. Lipid peroxide (LPO) is produced by the reaction of oxygen radicals with polyunsaturated fatty acids and can serve as a marker of OS in cerebral venous sinus thrombosis and stroke,[48] and can also be used for the differential diagnosis of stroke.

Nanomaterial antioxidants in stroke treatment

Nanomaterials are used for drug delivery in the treatment of diseases; some have antioxidant properties and can potentially scavenge ROS following stroke. Nanoparticle drug delivery systems can increase the blood concentration and half-life of drugs and protect neurons from OS-induced death in the ischemic brain.[107] In one study, macrophage-disguised honeycomb manganese dioxide nanospheres loaded with fingolimod reduced OS and alleviated the inflammatory response and neuronal death.[108] Nanomaterial antioxidants thus offer the possibility of multitargeted treatment of IS.

Regulation of OS and antioxidant defense system by methylene blue (MB)

Clinical applications of the redox dye MB include the treatment of methemoglobinemia, ifosfamide encephalopathy, and septic shock.[109] MB is also a potent guanylate cyclase inhibitor; in isolated hepatocytes and HeLa cells, MB was shown to inhibit ethanol-induced redox changes and fat deposition,[110] and its impact has been investigated in cultured human erythrocytes. However, the effects of MB on OS are controversial.[111] MB reduced OS in rats treated with cyclosporine A but increased intracellular OS at concentrations up to 5 μM in cultured endothelium cells.[112] MB can also be cytotoxic over the long term.[113] MB exposure induced OS caused by increased ROS levels and decreased CAT, SOD, SOD, and total cellular antioxidant levels.[114]

Conclusions

This review discussed the central role of OS as a bridge between aging and stroke, and the potential role of antioxidant enzymes, compounds, or molecules in stroke treatment. Despite the contribution of OS to the pathology of stroke, pharmacologic agents that alleviate OS have had limited benefit for stroke patients thus far. However, there are opportunities for the development of effective treatments for stroke using neuroprotective agents and multitargeted approaches. The combination of anti-OS, anti-inflammatory, and other agents is a promising future research direction.

Author Contributions

Shengjie Feng, Miaoxian Yang, Shengpeng Liu, Yu He: Conceptualization and design. Shengjie Feng, Miaoxian Yang: Writing, Original draft preparation and Editing. Ye Gong,Shuixiang Deng: Writing-Reviewing, Supervision and Validation.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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