The role of medical gas in stroke: an updated review

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Abstract

Medical gas is a large class of bioactive gases used in clinical medicine and basic scientific research. At present, the role of medical gas in neuroprotection has received growing attention. Stroke is a leading cause of death and disability in adults worldwide, but current treatment is still very limited. The common pathological changes of these two types of stroke may include excitotoxicity, free radical release, inflammation, cell death, mitochondrial disorder, and blood-brain barrier disruption. In this review, we will discuss the pathological mechanisms of stroke and the role of two medical gases (hydrogen and hydrogen sulfide) in stroke, which may potentially provide a new insight into the treatment of stroke.

Key words: stroke; medical gas; hydrogen; hydrogen sulfide; cell death

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Introduction

Medical gas is a large class of gases used in both clinical medicine and basic science research, including oxygen, hydrogen, carbon monoxide, carbon dioxide, nitrogen, xenon, hydrogen sulfide, nitrous oxide, carbon disulfide, argon, helium, and other noble gases.[1] Gas-based treatments are widely available clinically. For example, oxygen therapy for patients with dyspnea, nitrous oxide for analgesia and anesthesia, liquid nitrogen cryotherapy for secondary cellulitis, argon-helium knife therapy for liver cancer.[2-4] For decades, studies have found that certain medical gases possess neuroprotective properties leading to extensive interest.[5] Current research on neuroprotective gases focuses primarily on oxygen, xenon, hydrogen, hydrogen sulfide, nitric oxide, and argon, and their involvement with central nervous system diseases, such as stroke, traumatic brain injury, subarachnoid hemorrhage, and neurodegenerative disease, showing great translational potential.[6-11]

Stroke is the second leading cause of death, and one of the main causes of adult disability in the world, causing a heavy burden for medical and health care costs.[12,13] The two main subtypes of stroke include ischemic and hemorrhagic stroke. According to epidemiological statistics, 85% of strokes are categorized as ischemic, with the remaining 15% considered hemorrhagic. Tissue plasminogen activator (tPA) thrombolysis is the gold standard treatment and the only U.S. Food and Drug Administration-approved therapy for ischemic stroke.[14,15] However, the time-constrained therapeutic window greatly limits the use of tPA in acute ischemic stroke.[16] Although studies have shown that it is safe to administer intravenous thrombolytic drugs within 4.5 hours of stroke onset, thrombolysis treatment outside the therapeutic window is likely to cause complications, such as hemorrhagic transformation, reperfusion injury, and brain edema, with the former being the most feared complication.[17] Regarding hemorrhagic stroke, the current treatment is surgical removal of the hematoma, and reduction of intracranial pressure. However, this method can only prevent the deterioration of the disease, and has little effect in neurological recovery. It is apparent that current treatment of stroke is very limited. However, an increasing amount of recent studies have found the potential of blood-brain barrier (BBB) protection, stem cells, and medical gas in stroke therapy, offering new hope in the treatment of stroke.

It should be emphasized that research on the role of medical gases in stroke is receiving more and more attention, although their mechanisms of action differ. The thorough study of the relationship between medical gas and stroke will broaden horizons to guide the development of stroke treatment. In the present review, we will discuss the pathological mechanisms of stroke and advances in the research on the role of two medical gases (hydrogen and hydrogen sulfide) in stroke. We searched the researches in PubMed by the keywords "stroke" and "pathology" or "stroke" and "hydrogen" or "stroke" and "hydrogen sulfide."

Pathological Mechanisms of Stroke-Induced Brain Injury

The main subtypes of stroke include ischemic and hemorrhagic stroke. The former is caused by arterial embolism, in situ thrombosis, hemodynamic insufficiency, and branch occlusive disease. The latter is primarily caused by cerebral vascular rupture, including intracerebral hemorrhage and subarachnoid hemorrhage.[18,19] The common pathological changes of these

two types of stroke may include excitotoxicity, free radical release, inflammation, cell death, mitochondrial disorder, and BBB disruption. Herein, we will discuss these related mechanisms of brain damage after stroke.

Excitotoxicity

Excitotoxicity caused by glutamate is one of the most frequently studied pathological mechanisms of central nervous system diseases.[20-22] The process by which excess quantities of the excitatory neurotransmitter, glutamate, activates N-methyl-D-aspartate receptors (NMDARs) is a key step in the production of excitotoxicity.[23-25] After stroke, ischemia and hypoxia cause ion disorder in the neural cells, subsequently leading to cell depolarization and release of excitatory glutamate into the synaptic space. Thus, glutamate-induced NMDARs accumulation induces calcium inflow to the neurons.[26] Intracellular calcium overload leads to cell death by calpain activation, reactive oxygen species (ROS) generation, and mitochondrial damage.[27] In addition, there is evidence that excitotoxicity caused by glutamate can also be involved in brain damage following hemorrhagic stroke.[28] Many drugs targeting excitotoxicity presented an effective function in animal models of cerebral ischemia. For example, NDRG2 facilitates interstitial glutamate uptake to protect the brain from excitotoxicity after middle cerebral artery occlusion.[29] Glutamate oxaloacetate transaminase displays neuroprotection in ischemic stroke by reducing glutamate levels at the stroke site.[30,31]

Free radical release

Numerous experimental evidence indicates that in all forms of stroke damage, the formation of free radicals was increased, leading to nutritive oxidative stress.[32-34] There are several mechanisms of free radical production during ischemia, including intracellular calcium overload, mitochondrial dysfunction, NMDAR-mediated excitotoxicity, and release of inducible nitric oxide synthase.[35-38] Excessive free radicals, such as ROS and hydroxyl radical, can damage cellular macromolecules, and lead to autophagy, apoptosis, and necrosis of cells by affecting signaling pathways.[39,40] In addition, free radicals also cause DNA damage and cellular aging.[41,42] Based on these mechanisms, many free radical scavenging antioxidant therapies have been extensively studied.[43,44] For example, the iron chelator, deferoxamine mesylate, exhibits neuroprotection by inhibiting the formation of iron-induced hydroxyl radicals in various ischemic and hemorrhagic stroke animal models.[45] Melatonin, an effective free radical scavenger and antioxidant, shows neuroprotective effects in experimental models of hemorrhagic stroke.[46,47] However, since many free radicals are essential signaling molecules that contribute to normal neuronal function, related antioxidant therapy is required to only remove harmful free radicals without interfering with endogenous signaling.[48,49]

Inflammation

Inflammation is a key mechanism, contributing significantly to the pathophysiology and prognosis of stroke.[50] After stroke, a variety of agents, such as necrotic cells, impaired tissues, and free radical formation, are involved in the activation of inflammatory cells and trigger an inflammatory response.[51,52] In the early stages of inflammation, microglial cells are recruited and activated, converting to phagocytic cells.[53] Activated microglia not only release pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), but also play a neuroprotective role by the release of insulin-like growth factor I and brain-derived neurotrophic factor.[54-56] Later, neutrophils and monocytes cross the BBB into the ischemic area, which appears to be associated with cell adhesion molecules and chemokine signaling processes.[57-59] Moreover, the products of oxidative stress induce the expression of pro-inflammatory genes, such as nuclear factor kappa B (NF-κB), which increase the expression of cytokines and adhesion molecules, promoting the migration of leukocytes through brain endothelial cells.[60] Extensive research has shown that the inflammatory response after stroke not only causes brain tissue damage, but also participates in tissue remodeling after brain injury.[61] The latter seems to be an exciting area for translational research.

Cell death

In stroke, damage causes cell death through a variety of mechanisms, including apoptosis, necrosis, and autophagy.[62] Necrosis and apoptosis are the primary mechanisms.[63,64] Sodium pump failure, calcium overload, and excessive free radicals are involved in the induction of cell death. Apoptosis is a programmed cell death that terminates the cell's own life through signaling pathways such as mitochondrial signaling pathways, which can be induced by extracellular signals such as TNF-α, TRAIL (TNF related apoptosis inducing ligand) and Fas (CD95/APO1).[65-67] In animal models, some substances improve the prognosis of ischemic and hemorrhagic stroke through anti-apoptosis, including melatonin, Protein-L-isoaspartate (D-aspartate) O-methyltransferase, and Dl-3-n-butylphthalide.[68-70] Autophagy is another programmed cell death pathway, mediated by lysosomes, showing a two-sided effect in stroke. Several reports showed that excessive autophagy activation led to cell death, but many researchers have illustrated that appropriate autophagic activity is neuroprotective.[71-73] Studies have shown that autophagy may have the potential to protect the BBB integrity, demonstrating neuroprotection.[74] In addition, a large amount of cathepsin B release, caused by dysfunction of membrane trafficking after cerebral ischemia, can also induce cell death.[75]

Mitochondrial dysfunction

Growing evidence suggests that mitochondria regulates autophagy and apoptosis of cells.[76] Excitotoxicity and calcium overload lead to mitochondrial swelling during cerebral ischemia, triggering a cascade of cell death.[77] ROS produced by mitochondria also play a key role in brain damage following ischemic stroke.[78] Moreover, mitochondria regulate cell death at the level of protein modification by equilibrium fusion and fission.[79] For example, hyperglycemia promotes cell death following cerebral ischemia by inducing an increase in fission proteins dynamin-related protein 1, fission 1, and a decrease in fusion proteins optic atrophy 1 and mitofusin 2.[80]

BBB disruption

BBB destruction promotes stroke-induced brain damage, and causes complications, such as hemorrhagic transformation, playing an important role in stroke.[81] The immunoinflammatory reaction after cerebral ischemia can increase the production of matrix metalloproteins and myeloperoxidase, which may be the main contributor in the destruction of the BBB.[82] Furthermore, post-stroke changes in tight junction proteins, such as modification, translocation, and degradation lead to increased BBB permeability, which also worsens the prognosis of stroke.[81] Drugs have been investigated as a potential therapy in stroke recovery by improving BBB integrity.[83,84] For example, studies have found that baicalin attenuates brain injury after subarachnoid hemorrhagic by modulating BBB dysfunction and protecting BBB integrity.[85]

Other mechanisms

In addition to the above mentioned, the mechanisms of brain damage after stroke also include protein misfolding, reperfusion injury, innate and adaptive immune response, astrocytic changes, and white matter injury.[86,87] For example, misfolded proteins trigger the protein kinase R-like endoplasmic reticulum kinase pathway regulating eukaryotic initiation factor 2 kinase activation, which prevents new proteins synthesis after stroke.[88] Furthermore, changes in astrocytes after stroke affect the connection and signaling of neural activity, which may increase the damage of stroke and inhibit post-stroke recovery.[86] An exploration on the pathological mechanisms of stroke is conducive to pushing us closer to new potential therapies.

Advances in Research on the Role of Hydrogen and Hydrogen Sulfide in Stroke

Recently, the neuroprotective capacity of certain gases has received increasing attention. Among these gases, oxygen, hydrogen, hydrogen sulfide, NO, and some inert gases are probably the most studied gases. We will focus on the role of hydrogen and hydrogen sulfide in stroke and its related molecular mechanisms, and the research progress in recent years.

The role of hydrogen in stroke

Since it was often expressed as an inert gas in mammalian cells, it was previously thought that molecular hydrogen is nonfunctional in body cells.[89] However, the study by Ohsawa et al.[90] in 2007 indicated that hydrogen acts as an antioxidant to selectively reduce strong oxidants in cells, having a potential therapeutic effect in certain diseases. Since then, numerous studies have explored the role of hydrogen therapy in stroke. The mechanisms underlying the hydrogen-induced neuroprotection in stroke include anti-oxidative, anti-inflammatory and anti-apoptotic effects and changes in gene expression[91] (**Table 1**).

In animal experiments, hydrogen treatment significantly altered the survival and neurological function of animals after stroke. In a study by Nagatani et al.,[102] the 7-day survival rate of mice after bilateral common carotid artery occlusion was 8.3%, which significantly increased to 50% after inhalation of 1.3% hydrogen. Moreover, multiple studies have shown that the neurological function of mice that inhaled hydrogen is significantly improved after ischemic stroke.[103-105] In addition, hydrogen therapy also altered the morphology of brain tissue after stroke. Triphenyl tetrazolium chloride staining showed that hydrogen treatment reduced the infarction area after injury in stroke.[106-108]

Table 1: Mechanisms of neuroprotection of H_2 in stroke

Role of H_2 in stroke	Reference
Anti-oxidation	Ohsawa et al.,[90] Oharazawa et al.,[92] Ohta,[93] Cejka et al.,[94] Yuan et al.[95]
Anti-inflammation	Imai et al.,[96] Ning et al.,[97] Shi et al.,[98] Li et al.[99]
Anti-apoptosis	Li et al.,[99] Matei et al.[100]
Angiogenesis	Ergul et al.[101]

Note: H_2: Hydrogen.

As mentioned previously, the production of free radicals is an important pathological mechanism of brain damage after stroke. Currently, the most commonly studied neuroprotective mechanism of hydrogen therapy for stroke is that molecular hydrogen acts as a strong reducing agent to selectively scavenge certain free radicals in cells.[109] Hydroxyl radicals are considered the main trigger for free radical chain reactions.[110] In 2007, Ohsawa et al.[90] demonstrated that hydrogen selectively reduced hydroxyl radicals after the use of antimycin A. Another study showed that hydrogen eye drops directly decreased hydroxyl radicals in ischemia/reperfusion of retinas.[92] Hydrogen can also reduce 8-hydroxy-deoxyguanine, decreasing DNA oxidation.[93,111] Peroxynitrite is a strong biological oxidant which could induce neuronal death. The removal of peroxynitrite is related to hydrogen, so molecular hydrogen could directly reduce peroxynitrite to protect nerve cells.[94] Activation of nuclear factor erythroid 2-related factor 2 (Nrf2) exhibits reduced oxidative stress and neuroprotective properties, and has been identified as one of the goals of stroke therapy.[112] In addition, many studies have shown that hydrogen attenuates oxidative stress *via* Nrf2 pathway.[95,113,114]

Inflammation also plays an important role in stroke. Many studies have pointed out that hydrogen has an anti-inflammatory effect on cells.[115-117] In addition to antioxidant effects, the anti-inflammatory effects of hydrogen also play a non-negligible role in stroke.[118] Hydrogen may exhibit neuroprotection by reducing the number of microglia and astrocytes in damaged brain tissue, or by inhibiting activated microglia.[96,119] In the central nervous system, macrophages transformed by microglia can polarize to classic type (pro-inflammatory; M1-like) and alternative type (anti-inflammatory or protective; M2-like).[120,121] A recent study found that hydrogen treatment inhibits the increase in M1-like macrophages, but has no influence on M2-like cells, therefore implying anti-inflammatory effects in a stroke model.[97] In addition to cellular activation, hydrogen can also regulate gene expression of pro-inflammatory cytokines.[89,91] In most models, hydrogen treatment reduces the expression of pro-inflammatory factors such as IL-1β, IL-6, IL-10, TNF-α, interferon-γ, and NF-κB.[98,122] Hydrogen treatment also increases anti-inflammatory cytokines such as transforming growth factor-1β.[99]

Hydrogen therapy also shows anti-apoptotic properties.

Hydrogen treatment reduces the levels of miR-21, an effective anti-apoptotic factor.[99] In addition, hydrogen can induce angiogenesis, reduce cyclooxygenase-2 levels, and inhibit mitochondrial swelling under pathological conditions.[101,123] More mechanisms have yet to be studied.

Methods of ingesting molecular hydrogen include inhalation of hydrogen gas, oral ingestion by drinking hydrogen water, injection of hydrogen-saline, and topical application such as eye drops, bodywash, and cosmetics.[93] Hydrogen is not cytotoxic at any concentration, so hydrogen-based treatments are considered safe.[124] In addition, hydrogen has the advantage of being highly-selective reaction with ROS and rapidly diffusing, showing great potential in future stroke treatment.[90,92,125]

The role of hydrogen sulfide in stroke

In the past, hydrogen sulfide had always been considered a toxic gas that smelled of rotten eggs. However, later studies have found that endogenously produced hydrogen sulfide plays an important role as an important signaling molecule in the cardiovascular system and nervous system[126,127] (**Table 2**). Hydrogen sulfide is found in many organs and tissues, including the liver, blood, heart, and brain. A previous report has stated that the concentration of hydrogen sulfide within the brain is substantial.[128] Hydrogen sulfide is endogenously synthesized by cystathionine β-synthase, cystathionine γ-lyase, and 3-mercaptopyruvate sulfurtransferase.[129] Many studies have found that cystathionine β-synthase is ubiquitous in many areas of the brain, and may be the main hydrogen sulfide synthase in the central nervous system.[130-132] Current research suggests that the role of hydrogen sulfide in stroke is related to the concentration of administration; low concentrations of hydrogen sulfide may have neuroprotective effects on stroke, while high concentrations of hydrogen sulfide may cause neurotoxicity.[133]

Table 2: Mechanisms of neuroprotection of H_2S in stroke

Role of H_2S in stroke	Reference
Anti-inflammation	Wang et al.,[134] Seifert et al.[135]
Anti-oxidation	Qu et al.,[136] Kimura et al.[137]
Anti-apoptosis	Ji et al.,[138] Sen et al.[139]
Reduce protein misfolding	Wei et al.[140]

Note: H_2S: Hydrogen sulfide.

The mechanisms by which low concentrations of hydrogen sulfide exhibit neuroprotection in stroke include anti-inflammation, anti-oxidation, anti-apoptosis, and anti-endoplasmic reticulum stress.[141] Hypothermia has long been considered to have a protective effect through angiogenesis and anti-inflammation in brain damage, including stroke.[142-144] Blackstone and his colleagues[145,146] found that exposure to gaseous hydrogen sulfide at 80 ppm can reduce core body temperature, therefore illustrating the protective effects in fatal hypoxia in mice. Some researchers reported that slow release of hydrogen sulfide from donors inhibits inflammation-induced matrix metalloprotein-9, and thus reduces affected areas of transient middle cerebral artery occlusion mice.[134] Hydrogen sulfide also inhibits the release of nitric oxide, TNF-α, and IL-1β from astrocytes and microglia to achieve an anti-inflammatory effect.[135] In addition, free radicals and other reactive species can be scavenged by hydrogen sulfide, which may protect neurons from oxidative stress.[136,147] Kimura and his colleagues found that hydrogen sulfide could promote the activation of cystine/glutamate antiporter and increase the concentration of intracellular cystine, a substrate necessary for the generation and synthesis of glutathione.[137,148] As an important intracellular antioxidant, glutathione can scavenge ROS in mitochondria and protect neurons from oxidative stress. Inhibition of apoptosis is another role of hydrogen sulfide in stroke. In 2016, Ji et al.[138,149] reported that heat shock protein 70 could be up-regulated through the phosphoinositide 3-kinase/Akt/Nrf2 pathway and may prevent the recruitment of procaspase-9 by the apoptotic protease activating factor-1 apoptosome, thus inhibiting apoptosis. Moreover, hydrogen sulfide promotes the nuclear translocation of NF-κB, facilitating activation of anti-apoptotic gene.[139] As mentioned above, misfolding of proteins is also one of pathological mechanisms of stroke. Hydrogen sulfide may inhibit endoplasmic reticulum stress response by reducing protein misfolding *via* upregulation of the brain-derived neurotrophic factor-tyrosine protein kinase B pathway.[140] In addition, hydrogen sulfide also exhibits neuroprotective effects in stroke through other mechanisms, such as regulating calcium concentration or facilitating long-term potentiation.[150]

The high concentration of hydrogen sulfide is neurotoxic, and may be associated with inhibition of mitochondrial respiration.[151] Current research suggests that hydrogen sulfide can inhibit mitochondrial oxidative phosphorylation by inhibiting cytochrome C oxidase (complex IV).[152,153] It has also been reported that hydrogen sulfide may activate NMDA receptors, leading to calcium overload, and enhancing receptor-mediated glutamate excitotoxicity in stroke.[154,155]

Although there are no clinical trials with direct evidence suggesting that hydrogen sulfide has neuroprotective effects, it has been reported that plasma hydrogen sulfide levels below a certain level positively correlate with the prognosis of stroke in patients.[150] Animal experiments have also shown a slight increase in plasma hydrogen sulfide levels in transient middle cerebral artery occlusion or permanent middle cerebral artery occlusion mice.[134,156] Therefore, the role of hydrogen sulfide in stroke is worthy of recognition, and is expected to show translational potential in the future. However, it should be noted that high concentrations of hydrogen sulfide are toxic, leading to respiratory failure, nerve dysfunction, brain edema, and disturbance of consciousness, which is one of the problems that should be addressed in the future (**Figure 1**).[157,158]

Future Perspectives and Translation

Through extensive experimental studies in animal models of stroke, we have found that hydrogen and hydrogen sulfide are important signaling molecules that exhibit neuroprotection in stroke through various mechanisms. Specific mechanisms include anti-oxidation, anti-inflammation, anti-apoptosis, etc. In summary, medical gases, including hydrogen and hydrogen sulfide, play a significant role in stroke. However, some

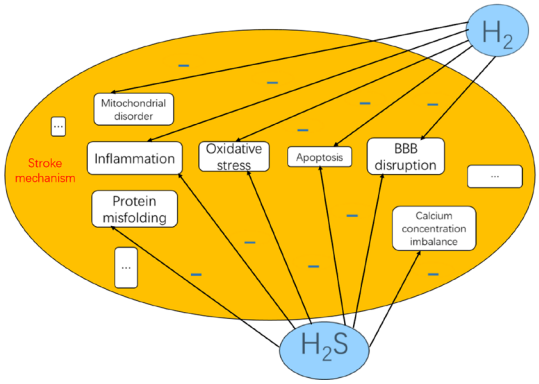

Figure 1: Major mechanisms of H_2 and H_2S in stroke.
Note: H_2 and H_2S exert neuroprotective effects in stroke through various mechanisms. H_2: Hydrogen; H_2S: hydrogen sulfide; BBB: blood-brain barrier.

important issues have not been resolved, such as insufficient clinical evidence, cytotoxicity of hydrogen sulfide, occurrence of complications, methods of administration and dosage, and combined use of drugs. Therefore, more animal experiments and clinical trials are needed to establish the standard of use of medical gases, to clarify the exact mechanism of medical gas therapy, and to ensure the safety of treatment. We believe that medical gases are expected to be an important complementary therapy for stroke in the future.

Author contributions
Study design: SC, ZYZ; literature search: ZYZ; manuscript preparation and writing: ZYZ; manuscript revision and editing: YJF, SC, CL, YJL; figures and tables preparation: ZYZ, YJF; manuscript review: SC, JMZ. All authors approved the final manuscript for publication.
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