Potential application value of xenon in stroke treatment

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Abstract

Stroke is an acute disease with extremely high mortality and disability, including ischemic stroke and hemorrhagic stroke. Currently only limited drugs and treatments have been shown to have neuroprotective effects in stroke. As a medical gas, xenon has been proven to have neuroprotective effect in considerable amount of previous study. Its unique properties are different from other neuroprotective agents, making it is promising to play a special therapeutic role in stroke, either alone or in combination with other treatments. In this article, we aim to review the role of xenon in the treatment of stroke, and summarize the mechanism of using xenon to produce therapeutic effects after stroke according to the existing research. Moreover, we intend to explore and demonstrate the feasibility and safety of xenon for clinical treatment of stroke. Despite the disadvantages of difficulty in obtaining and being expensive, as long as the use of reasonable methods, xenon can play an important role in the treatment of stroke.

Key words: stroke; xenon; ischemia; neuroprotective effects; brain diseases

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Introduction

Stroke, a sudden neurological deficit caused by vessel dysfunction, is a clinical syndrome rather than a single disease.1 Usually, there are two types of stroke, ischemia stroke (55–90%) and hemorrhagic stroke (12–35%).2 Subarachnoid hemorrhage is a special type of hemorrhagic stroke because of its significant morbidity and mortality rate,3 although it accounts for only 5% of stroke.4 According to the report, stroke is the fifth cause of death in America and become the leading medical cause of acquired adult disability worldwide.5,7 Especially in low and middle income countries, the incidence of stroke continues to increase—accounting for 85% of global stroke burden.8 In China, it was reported that 837,300 urban residents and 1,023,400 rural residents died from stroke in 2014 alone.9 So far, plenty of studies have been conducted, intend to improve the prognosis of stroke and many substances as well as therapies have been discovered and applied.10 Among them, medical gas has received the attention of researchers because of its special physical properties.11,12

Recently, many studies suggest that a variety of medical gases may serve as neuroprotective agents against stroke.13 Xenon is an odorless and colorless noble gas,14 which was firstly used in surgical anesthesia by Stuart C. Cullen and Gross in 1951.15,16 As a kind of volatile anesthetics, xenon has been studied decades because of its potential value in neuroprotective area. Plenty of previous research has shown that xenon can play a protective role in models of hypoxic-ischemic insults, as well as subarachnoid hemorrhage.17-20 In this article, we intend to summarize the role of xenon in stroke and its mechanisms as well as the possible clinical application forms based on current research.

Mechanism of Protective Effects of Xenon in Stroke

The most widely studied and well-known mechanism of xenon in neuroprotective area is N-methyl-d-aspartate (NMDA) receptor glycine site antagonism.21 By interacting with the aromatic ring of phenylalanine 758,22 xenon can binds to the NMDA receptor as other anesthetic gas such as isoflurane. Unlike isoflurane, helium has a non-competitive inhibition in addition to competitive inhibition.23

NMDA receptor is one of the two subtypes of ionotropic glutamate receptors, the another one is α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor. After stroke, multiple factors include lack of oxygen and nutrients, protein function damage lead to the accumulation of excitatory glutamate in extracellular space,24 which result in the over-activation of NMDA receptor. This process was called excitotoxicity and has been considered as one of the most important mechanisms of nerve injury after stroke.25,26

Once the NMDA receptor was activated, excessive Na+ and Ca2+ can flux into the cell, activate a series of downstream pathways. Such as the activation of calpain,27 nitric oxide (NO) production,28 generation of reactive oxygen species (ROS).29,30 Further causes of neuronal cell dysfunction and death are diverse, including but not limited to mitochondrial damage, DNA damage, cell membrane destruction.

However, several NMDA receptor antagonists has failed to show efficacy in clinical trials.31 The main possible factors affecting the efficacy are the following two points. According
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to the receptor location hypothesis, activation of NMDA receptors can trigger pro-survival or pro-death signaling depending on the subcellular locations or subtypes of NMDA receptors. Most NMDA antagonists could not target on the extrasynaptic NMDA receptor, which result in these antagonists produce adverse side effects or even neurotoxicity at neuroprotective concentrations. Moreover, for these agents, it is too hard to achieve the brain damage area immediately because of the existence of the blood-brain barrier (BBB). This makes the peak of drug concentration could not appear simultaneously with the peak of glutamate in the extracellular space, while it has been proved that delayed and prolonged blockade of NMDA receptors might be harmful. As a low-affinity use-dependent NMDA receptor antagonist, xenon has low blood-gas partition coefficient which is 0.115. Moreover, xenon can quickly pass the BBB after inhalation. These characteristics allow xenon could rapidly accumulate in the stroke area and be rapidly metabolized by the body when the administration is stopped. For the same reasons, xenon was also used in anesthesia.

In addition to blockade of NMDA receptors, another mechanism by which xenon plays a therapeutic role in stroke is the activation of two-pore domain potassium channel TWIK-related K+ channel-1 (TREK-1). The study which was held by Gruss et al. showed that at the concentration of 60% for xenon, 25% of TREK-1 was activated. Formal experiments have shown that TREK-1 channel has neuroprotective properties in ischemia.

TREK-1 is a background potassium channel existed throughout the central nervous system, and is a member of two-pore-domain potassium channels family. The open of TREK-1 in the physiological range lets potassium ions out of the cell membrane, increases the negative charge in neurons and therefore contributes to the background as well as opposes depolarizing influences. By opening TREK-1 channel, xenon is able to inhibit the activation of voltage-dependent Ca2+ channels on the presynaptic membrane, which usually induce the release of glutamate after stroke, as well as enhance the blocking of NMDA receptors. By this way, xenon further suppressed the development of excitotoxicity (Figure 1).

Another possible mechanism found by Bante et al. and his colleague is the activation of adenosine triphosphate-sensitive potassium (K+ATP) channel, which was considered play a key role in neuroprotective pathways. The pore-forming subunit Kir6.2 of K+ATP channel was found has a protective effect in ischemic brain injury. Traditional K+ATP channel openers including nicorandil and diazoxide could not penetrate through the BBB, which limits their implication in neuroprotective area. Compared with other K+ATP channel openers, xenon can diffuse through the BBB easily and is able to activate the K+ATP channel without the help of Mg2+. Moreover, xenon enhanced the K+ATP current by highly specific activate the Kir6.2 subunit, which means the effect of xenon is direct and precise.

In subarachnoid hemorrhage (SAH), it was found that xenon-treated animals presented with a milder damage, especially in the hippocampus, CA3 as well as dentate gyrus (DG). The possible mechanism postulated by Veldeman et al. is that xenon can reduce microglial activation by some still unknown immunomodulatory pathway. It has been proved that microglia activation inflicts delayed brain injury after subarachnoid hemorrhage. The NMDA receptor on microglia was presumed to be the trigger of this pathway and there is some evidence to support this hypothesis.

There are also some other biological effects of xenon in the central nervous system that have not been proven in stroke. Shichino et al. showed that in early stage, xenon induced an initial increase in acetylcholine release while it was a gradual decrease later, which means that xenon can act on not only receptors but also the neurotransmitter. Franks et al. found that xenon inhibited calcium ATPase pump activity in rat brain synaptic plasma membranes, resulting in an increase in neuronal Ca2+ concentration and a decrease in neuronal excitability. It was also reported that xenon reduced whole-brain metabolic rate of glucose as well as regional cerebral blood flow, which may have help in the reduction of Intracranial pressure and enhance the brain protection effect.

**Experimental Studies of Nitrous Oxide in Stroke**

Since xenon is proved to be an NMDA antagonist, a considerable amount of study has been brought out to find out whether xenon has neuroprotective function or not. As the most important and unique disease in neurological diseases, the role of xenon in stroke has attracted growing attention of researchers. Most experiments have demonstrated the protective role of xenon in stroke, whether in ischemia or hemorrhage. But there are also some experimental results that are contradictory. It was discovered that xenon can inhibit the catalytic efficiency of tissue plasminogen activator (tPA), which is widely used in the treatment of ischemia stroke. Because of this mechanism, xenon has been proven to be unsuitable to be used with tPA at the same time in the treatment of ischemic stroke. However, tPA also has side effects such as the BBB disruption in the acute stroke. It was also shown that xenon can help prevent from the hemorrhage as well as BBB dysfunction induced by tPA when it was used after ischemic. As other anesthetic gases do, xenon has the function of lowering body temperature. As it was proved that therapeutic hypothermia
is a promising treatment of stroke, some researchers intend to find out whether xenon can exert a synergistic effect with hypothermia in stroke (Table 1).

**CLINICAL STUDIES**

Despite the lack of direct clinical trials of xenon in the treatment of stroke patients, several related clinical studies have yielded encouraging results. Laitio et al. from Turku University Hospital have conducted a randomized clinical trial to figure out the role of xenon in brain ischemia damage in cardiac arrest patients. 110 patients who had experienced out-of-hospital cardiac arrest were randomly assigned to receive hypothermia treatment alone or either inhaled xenon combined with hypothermia for 24 hours. According to this research, patients who inhaled xenon combined with hypothermia have less damage in white matter compared with those patients who received hypothermia treatment alone. It was also proved that xenon combined with hypothermia is feasible in the treatment of brain ischemia and has favorable cardiac features. Another common condition of cerebral ischemia and hypoxia is in newborns. Investigators from University of Bristol and St Michael’s Hospital have conducted a clinical trial to examine the treat effect of inhaled xenon in the newborn infants with hypoxic-ischemic encephalopathy in combination with cooling (ClinicalTrials.gov, NCT02071394). It was assumed that the xenon plus cooling will produce better neuroprotection than the standard treatment of cooling alone in newborn infants. Yet there are no clinical studies to prove this, in vitro experiments from rats and newborn pigs have confirmed this hypothesis. The combination of xenon and therapeutic hypothermia is a promising therapy in brain ischemia and hypoxia.

**GAS DELIVERY METHODS**

As a kind of trace element in atmosphere, it is extremely expensive to separate xenon from air and it is still impossible for Industrial synthesis for now. As the result, the cost of xenon is around 10 $/L and the price of inhaling xenon is 150$/h, far higher than other anesthetic gases or neuroprotective agents. High prices and low yields are two important reasons hindering the clinical application of xenon. Dr. Dingley et al. from Swansea University has built up a closed-circuit xenon delivery system which can recirculate gases, remove CO2 and add O2 at the same time. Since xenon can be recycled in this system, with the help of this gas transmission route, the cost of applying xenon is greatly reduced. It was also reported that standard anesthesia workstation can be used to delivery xenon in a closed-circuit, although its pharmacokinetics still needs further exploration.

Another promising method to deliver xenon is the use of echogenic liposomes (ELIP). Xenon can be encapsulated into ELIP with the help of pressurization-freeze method. After Intravenous injection of Xenon-ELIP, ultrasound can be used to trigger Xenon release into the internal carotid artery. The use of this technology can effectively transmit xenon into the central nervous system with higher efficiency and better targeting. It has been reported that in ischemic stroke, use of Xenon-ELIP in 5 hours can significantly reduce the infract size, the dose range of the maximum therapeutic effect is of 7–14 mg/kg. Similar, Xenon-ELIP also exerts a great neuroprotective effect in the model of subarachnoid hemorrhage.

**CONCLUSION AND FURTHER STUDIES**

It has been proved that xenon has a bright future in the treatment of stroke. Despite the lack of sufficient clinical evidence, due to its unique chemistry properties and excellent performance in various experiments, we have reason to believe that xenon can play an important role in stroke therapy. However, there are still many difficulties that need to be further over-

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**Table 1: Study on the role of xenon in stroke**

| Study       | Year | Animal Model | Results                                                                 |
|-------------|------|--------------|--------------------------------------------------------------------------|
| Veldeman et al. | 2017 | Sprague-Dawley rats SAH | Xenon reduces the hippocampal neuronal cell loss and decreases the cortical microglial cell activity. |
| Sheng et al. | 2012 | C57BL/6 mice ICH | Xenon decreases brain edema, microglial activation, hydrocephalus and neurologic deficits in collagenase-induced ICH. |
| Limatola et al. | 2010 | C57BL/6 mice MCAO | Xenon dose dependently inhibits tPA-induced thrombolysis and the reduction of ischemic brain damage during the ischemic while suppress brain damage and tPA-induced brain hemorrhages after the ischemia. |
| David et al. | 2010 | Sprague-Dawley rats MACO | Xenon preconditioning improves histological and neurological functional outcome in both gender in a stroke model of mice. |
| David et al. | 2008 | Sprague-Dawley rats MCAO | Xenon reduces cortical neuronal death and brain temperature while enhance the motor coordination and rearing activity at the same time. |
| Hobbs et al. | 2008 | Seven-day-old Sprague-Dawley rats HIE | Xenon and hypothermia combine additively offered long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. |
| Martin et al. | 2007 | Seven-day-old Sprague-Dawley rats HIE | Asynchronous administration of xenon and hypothermia significantly reduces brain infarction. |
| Ma et al. | 2005 | Seven-day-old Sprague-Dawley rats HIE | Combination of xenon with mild hypothermia has neuroprotective effect through the antiapoptotic mechanism in hypoxic-ischemia-induced brain injury. |
| Homi et al. | 2003 | C57BL/6 mice MCAO | Xenon reduces the infarct volume as well as improve the neurologic scoring. |
| David et al. | 2003 | Sprague-Dawley rats MCAO | Xenon at 50 vol% reduces ischemic neuronal death in the cortex while it exhibits potentially neurotoxic effects at a higher concentration (75 vol%). |

Note: SAH: Subarachnoid hemorrhage; MCAO: middle cerebral artery occlusion; ICH: intracranial hypertension; HIE: hypoxic ischemic encephalopathy; tPA: tissue plasminogen activator.
came. Firstly, the production process of xenon is too complicated, as well as the method of clinical use. Secondly, the exact mechanism of action and the molecular biology pathway of xenon in stroke and neuroprotection, remains to be further studied. Last but not least, a large number of clinical trials and data are still needed to demonstrate the effectiveness and safety of xenon in stroke.

**Author contributions**

CSZ was responsible for writing the manuscript. HL was responsible for its revision. ZW and GC were responsible for its drafting and revision. All the authors read and approved the final version of the manuscript for publication.

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