The role of nitrous oxide in stroke

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Abstract

Stroke that is caused by poor blood flow into the brain results in cell death, including ischemia stroke due to lack of blood into brain tissue, and hemorrhage due to bleeding. Both of them will give rise to the dysfunction of brain. In general, the signs and symptoms of stroke are the inability of feeling or moving on one side of body, sometimes loss of vision to one side. Above symptoms will appear soon after the stroke has happened. If the symptoms and signs happen in 1 or 2 hours, we often call them as transient ischemic attack. Moreover, hemorrhagic stroke often leads to severe headache. It is known that neuronal death can happen after stroke, and it depends upon the activation of N-methyl-D-aspartate (NMDA) excitatory glutamate receptor which is the goal for a lot of neuroprotective agents. Nitrous oxide was discovered by Joseph Priestley in 1772, and then he and his friends, including the poet Coleridge and Robert Sauce, experimented with the gas. They found this gas could make patients loss the sense of pain and still maintain consciousness after inhalation. Shortly the gas was used as an anesthetic, especially in the field of dentists. Now, accroding to theme of Helene N. David and other scientists, both of nitrous oxide at 75 vol% and xenon at 50 vol% could reduce ischemic neuronal death in the cortex by 70% and decrease NMDA-induced Ca^{2+} influx by 30%. Therefore, more clinical and experimental studies are important to illuminate the mechanisms of how nitrous oxide protects brain tissue and to explore the best protocol of this gas in stroke treatment.

Key words: nitrous oxide; experimental research; clinical research; ischemia; neuroprotective effects; anesthetics

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Introduction

Stroke is defined as a sudden neurological pathological sign and always has been considered as a significant leading factor of death and disability in the world.[1] The high morbidity and mortality of this catastrophic illness make our society and family bear a huge burden[2]; what's more, what is causing it becomes a public health issue and wait to settle pressingly. In addition, with increasing of population in many industrialized countries, the severity of stroke rise up year by year, therefore this problem must be thought highly by all of us. Generally speaking, stroke can be divided into ischemic accounting for approximate 80% of them and hemorrhagic stroke.[3] Currently many studies have shown that it is nitrous oxide at subanesthetic concentrations that may have larvaceously neuroprotective and therapeutic characters, so we can focus on their beneficial effects to settle the issue of ischemia-induced neuronal death.[4]

Nitrous oxide is the most commonly used anesthetic that has been used for the inhalation and maintenance of anaesthesia for over 160 years, because of low cost, low tissue solubility, and low rate of cardiorespiratory complications. Nitrous oxide that is a relatively weak anaesthetic gas should need to be inhaled in high concentrations which restrict oxygen delivery (such as a common mixture is 30% oxygen with 70% nitrous oxide).[5] Many studies have shown that the nitrous oxide metabolic effects are linked to elevated

plasma homocysteine levels and endothelial dysfunction perioperatively,[4,6] and nitrous oxide may possess potentially neuroprotective ability in animal models.[4,7] However, nitrous oxide also has neurotoxic and pro-neurotoxic action under other certain conditions,[8-11] so in this article, we will discuss the influence of nitrous oxide for stroke injury and the potential mechanisms on the basis of experimental and clinical studies to explore the feasibility of treatment.

Mechanism of Nitrous Oxide in Stroke

Glutamate is a common neurotransmitter that plays an important role in many physiological functions.[12] However, under a lot of pathological conditions, neurons will become so sensitive to glutamate, and the glutamate also can damage or kill them, mainly through N-methyl-D-aspartate (NMDA) receptor that can mediate calcium influx,[13] Blocking the NMDA receptor which always be thought to be inhibited by nitrous oxide and then excitotoxicity may help to decrease damage and dysfunctions of central nervous system to avoid disorders.[14] With many investigations, nitrous oxide and xenon, which are safe anesthetics, have been demonstrated to be effective inhibitors of the NMDA receptor,[15-17] and to have a pharmacological character that resembles as NMDA receptor antagonist in low-affinity use.[17] The gases could cross over the blood-brain barrier, and has low blood/gas solubility that is propitious in terms of rapid absorbed and expelled (conditions that may be beneficial for treatment and reduce risk of neurotoxicity), so the nitrous oxide have been recently shown to possess therapeutic characters (**Figure 1**).[4]

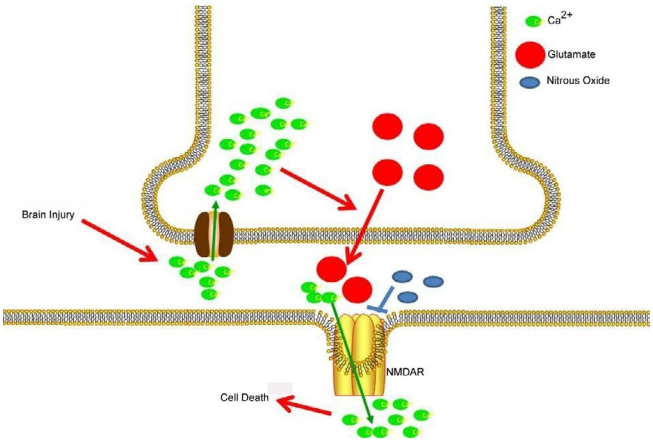

Figure 1: The mechanisms of nitrous oxide in the stroke.
Note: NMDAR: N-methyl-D-aspartate receptor.

Experimental Studies of Nitrous Oxide in Stroke

As for animal experiment, animal models of hemorrhagic and ischemic stroke, especially ischemic stroke, were successfully established, then the gas of nitrous oxide was applied to treat the subject after stroke insult, and finally the researchers detected the effects of nitrous oxide on stroke and explored the potential mechanisms by which the gas protected nervous system. As we known, animal experiment belongs to basic medical research or preclinical research and most of them were aimed to investigate the mechanism of objective gas in neurological influence following stroke. The conclusion of these studies may be different owing to different experimental conditions and methods. We analyze several recent experimental studies related to this gas for stroke treatment in this paper (**Table 1**), and summarize the outcomes.

So after analyzing of the above experimental results, the effect of nitrous oxide to neuropsychological functions has been some areas of controversy, so do in animal models. Some research has already demonstrated preferable outcomes, while others show detrimental results.[7,21,24,25] Unfortunately, only a little of randomized controlled experiment have illustrate functional outcomes. Most of them were limited to neurological outcome, according to cardiopulmonary bypass.[26-28] In theory, nitrous oxide can increase rate of cerebral metabolism, cerebral blood flow, and intracranial pressure.[29] Nitrous oxide also has the potential to give rise to intracranial air volume.[30,31] However, many studies demonstrate that nitrous oxide at 75 vol% and xenon at 50 vol% can reduce cortical brain damages *in vivo*, and decrease NMDA-evoked Ca^{2+} influxes of neuronal cell, which is a process which is considered as a major primary event involved in the excitotoxic neuronal death.[32] The neuroprotective action of nitrous oxide at 75 vol% and of xenon at 50 vol% after middle cerebral artery occlusion (MCAO) *in vivo* may account for their pharmacologically antagonistic properties at the NMDA receptor,[33] because the gas have no effect to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.[17] So many dates of studies have shown that nitrous oxide and xenon keep normal cells from excitotoxic neuronal death produced by stimulating either glutamate or NMDA in cortical cell cultures.[34] The neuroprotective effects of nitrous oxide were found at subanesthetic concentrations corresponding to 0.6 minimum alveolar concentration, which did not bring suppression of locomotor activity, as assessed by the observation of the behavior of the freely moving animals.[18] These protective effects of nitrous oxide manifest to be timing-sensitive, and with a relative narrow therapeutic window that exists within 2 hours following MCAO. When administered at 3 hours after MCAO, nitrous oxide increased infarct volume, appearing to be neurotoxicity.[18] Based upon these facts, we believe that nitrous oxide at 75 vol% and of xenon at 50 vol% may be beneficial for the stroke of treatment of human.

Table 1: The neuroprotective effects of hydrogen nitrous oxide in stroke

Study	Model	Main results	Animal/cells
David et al.[7]	MCAO	At 75 vol%, nitrous oxide significantly reduced NMDA-induced Ca^{2+} influx in cortical cell cultures, and reduced ischemic neuronal death in the cortex.	Rats
Haelewyn et al.[18]	MCAO	After rats subjected to transient cerebral ischemia, nitrous oxide offers full neuroprotection after ischemia onset at 50 vol% both in the histologic and neurologic outcome levels when administered over 2 hours, but not 3 hours.	Rats
Abraini et al.[4]	MCAO	Postischemic subanesthetic nitrous oxide alone and intraischemic nitrous oxide-isoflurane have been attributed to a proapoptogenic interaction between isoflurane and nitrous oxide.	Rats
Bedforth et al.[19]	MCAO	The addition of 50% nitrous oxide to the 2.2%, but not the 3.4% concentrated sevoflurane enhanced middle cerebral artery blood flow velocity and reduced autoregulatory indices significantly.	Human
Yokoo et al.[20]	MCAO	Intraischemic nitrous oxide in rats anesthetized with isoflurane was found to improve neither histologic nor neurologic outcome produced by MCAO.	Rats
Abraini et al.[21]	MCAO	Postischemic treatment with nitrous oxide alone *vs.* intraischemic treatment with nitrous oxide in the presence of isofluran	Rats
Bruder[22]	ICH	Nitrous oxide should be avoided in patients with severe ICH or during emergency surgery.	Human
Sugaya et al.[23]	CCAO	Nitrous oxide drastically reduced the protective effect of isoflurane incurred accidentally during anesthetic management.	Rats

Note: MCAO: Middle cerebral artery occlusion; NMDA: N-methyl-D-aspartate; ICH: intracranial hypertension; CCAO: common carotid artery occlusion.

Clinical Studies of Nitrous Oxide in Stroke

A *post hoc* analysis of a subset of data, which comes from the intraoperative hypothermia for aneurysm surgery trial, showed that the use of nitrous oxide in neurosurgery was associated with an increasing risk of developing delayed ischemic neurological deficits in patients with cerebral aneurysms, but with absence of longterm gross neurologic or neuropsychological damage.[35] Counter-intuitively, the patients that inhaled nitrous oxide were also at risk for neuropsychological impairment on at least one test.[36] In addition, as same to other anesthetics, nitrous oxide can cause hypothermia,[37] which can downregulate the release of glutamate, glycine and so does inhibit oxidation.[38]

Possible Therapeutic Implications

According to the data of the present studies, there are an increasing number of evidences that nitrous oxide and xenon may have potentially neuroprotective and therapeutic abilities for the treatment and be beneficial for protection of brain tissue, even if xenon at concentrations of 75 vol% further appear to be potentially neurotoxic properties and adverse side effects. In contrast, xenon at 50 vol% will reduce neuronal cells death, when administered as post-treatment after MCAO in the rat, and it will reduce NMDA-evoked Ca^{2+} influxes in neuronal cell cultures; accordingly, xenon at an about concentration (approximately 40 vol%) could be considered as a potentially therapy for the treatment of stroke in humans. Now, what is the most major reason is that clinical use of xenon is the expensive cost of production, but we think combination of both of nitrous oxide and xenon will solve this problem. Finally we believe that nitrous oxide will open up a new path to protect the nervous system.

Author contributions

ZWZ and DPZ were responsible for writing the manuscript. HYL 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.

Conflicts of interest

The authors declare that they have no competing interests.

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