Anti-inflammatory signaling: the point of convergence for medical gases in neuroprotection against ischemic stroke

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Abstract

Recent studies suggest that a variety of medical gases confer neuroprotective effects against cerebral ischemia, extending function beyond their regular clinical applications. The mechanisms underlying ischemic neuroprotection afforded by medical gases have been intensively studied over the past two decades. A number of signaling pathways have been proposed, among which anti-inflammatory signaling has been proven to be critical. Pursuit of the role for anti-inflammatory signaling may shed new light on the translational application of medical gas-afforded neuroprotection.

Key words: ischemic stroke; ischemic brain injury; medical gas; anesthetic gas; inflammation; neuroprotection; preconditioning; inflammatory signaling

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Introduction

Medical gases, such as oxygen, carbon dioxide, nitric oxide (NO) and carbon monoxide (CO) are commonly used as medical tools to help patients breathe easier, to facilitate medical diagnosis or to function as an anesthetic or analgesic agent (Deng et al., 2014). Remarkably, recent studies suggest that a variety of medical gases may also serve as neuroprotective agents against cerebral ischemia in a manner distinct from their regular uses (Chen et al., 2014; Ginsberg, 2016). The ready availability of these medical gases bedside renders them a viably translatable focus for stroke treatment, already attracting a considerable amount of studies (Deng et al., 2014). Although the underlying protective mechanisms afforded by medical gases against cerebral ischemia still remain obscure and may involve multiple pathways that reflect the complexity of stroke pathology (Baxter et al., 2014; Gonzalez-Moreno et al., 2014; Poittevin et al., 2014; Seifert and Pennypacker, 2014), current evidence has suggested that the actions of these medical gases may converge on inflammatory signals (Chen et al., 2015; Xiong and Yang, 2015).

Hydrobaric Oxygen (HBO)

HBO is a nondrug and noninvasive treatment that has been widely used in clinical practice for many diseases, including acute CO poisoning (Weaver et al., 2002), gas gangrene (Rocek-Wiedmann et al., 2005), decompression sickness (Bennett et al., 2012). With the capability to relieve cerebral hypoxia, HBO attenuates cerebral vaso-spasm (Hald and Alford, 2014; Hasegawa et al., 2015), a condition highly detrimental for patients suffering from subarachnoid hemorrhage (Cheng et al., 2015; Guresir et al., 2015). HBO confers protection against cerebral ischemic stroke, as illustrated by a number of studies (Lee et al., 2013; Ding et al., 2014; Stetler et al., 2014).
Molecular Hydrogen ($H_2$)

$H_2$, an inert and non-functional molecule that normally exists in our body, also acts as a neuroprotective agent against cerebral ischemia (Ohta, 2014), with multiple studies demonstrating that $H_2$ impacts ischemic inflammatory signaling (Buchholz et al., 2008; Cai et al., 2013; Li et al., 2013). $H_2$ directly attenuates inflammation by inhibiting nuclear factor kappa B (NF-kB) pathway activation (Chen et al., 2010), NO formation, tumor necrosis factor alpha (TNFα)-induced IL-6 and intercellular cell adhesion molecule-1 (ICAM-1) mRNA expression (Buchholz et al., 2008; Cai et al., 2013; Li et al., 2013) and downregulating the expression of chemokine (C-C motif) ligand 2 (CCL2), interferon (INF)-γ, and prostaglandin E2 (PGE2) (Kawasaki et al., 2010), all of which are important inflammatory molecules that contribute to ischemic and hemorrhagic brain injury (Ansar et al., 2014; Pennypacker, 2014; Shimamura and Ohkuma, 2014; Brown et al., 2015; Wu et al., 2015; Xiong and Yang, 2015). In addition to a direct impact on inflammatory signaling molecules, $H_2$ also affects oxidative stress and thus regulates inflammation indirectly. $H_2$ reduces oxidative stress by inducing anti-oxidation systems, including hemeoxygenase-1 (HO-1), superoxide dismutase (SOD), catalase and myeloperoxidase (Huet et al., 2016). In particular, the up-regulated HO-1, a microsomal enzyme that degrades heme to CO, free iron, and biliverdin (Cremer et al., 2014), functions as an important signal bridging oxidative stress and inflammation. Nrf-2 is a transcription factor with pleiotropic capacity and recruits multiple pathways aiming at reducing brain damage after intracerebral hemorrhage (Zhao and Aronowski, 2013). The activation of Nrf-2 can coordinate and regulate a number of oxidative stress-induced signals, such as HO-1 (Ishii et al., 2000). Additionally, HO-1 can feedback onto Nrf2 by modulating the subcellular distribution and activation of Nrf2 (Biswas et al., 2014).

CO

CO is a soluble gas generated almost exclusively through the degradation of heme by hemeoxygenase (HO) enzymes, including HO-1 (Xiong et al., 2014). Mice exposed to low concentrations of CO after permanent ischemia experience less severe brain damage and attenuation of neurological deficits (Wang et al., 2011; Oh and Choi, 2015). As we have mentioned, HO-1 can be induced by Nrf2 and thus bridges the regulation of oxidative stress to the regulation of inflammatory signals (Ishii et al., 2000; Biswas et al., 2014). Together with NO, CO can also be synthesized from L-arginine by the catalytic reaction of NO synthase (NOS) (Nathan, 1992). NO is a highly reactive free radical that plays important roles in the regulation of vascular and immune functions, anti-apoptosis and neurotransmission by producing cyclic guanosine monophosphate (cGMP), nitrosyl iron complexes, and S-nitrosothiols (Chung et al., 2008). Similar to NO, CO also has potent immunomodulatory capabilities and thus can potentially impact the corneal inflammatory response (Patil et al., 2008). Generation of CO in microglia is essential for effective elimination of blood and heme after subarachnoid hemorrhage that may otherwise lead to neuro-inflammation (Zhao et al., 2015) and neuronal loss (Schallner et al., 2015; Ma et al., 2016). Notably, most of the studies describing CO as a neuroprotective gas use a relatively low dose. It needs to be remembered that higher concentrations of CO are potently neurotoxic and can result in memory loss, confusion and even more severe symptoms in and of itself.

NO

NO has dual effects during different phases of ischemic injury depending on the expression of different NOS enzyme isoforms, which include inducible NOS (iNOS), neuronal NOS (nNOS) or endothelial NOS (eNOS) (Iadecola, 1997). Upon cerebral ischemia, NO concentration decreases, while immediately after reperfusion, NO biosynthesis is triggered by overactivation of nNOS (Ito et al., 2010). After 12 hours of reperfusion, the level of NO increases again due to the induction of iNOS expression (Khan et al., 2005). At this stage, NO is derived from different sources, including microglia (Khan et al.,
2005), astrocytes (Gibson et al., 2005), endothelial cells (Niwa et al., 2001), infiltrated leukocytes (Suzuki et al., 2002) and also neurons (Zhou and Zhu, 2009). NO from different sources may exert an influence on the evolution of brain damage at different time-points after an ischemic insult (Iadecola et al., 1997). nNOS inhibition reduces excitotoxicity (Yu et al., 2008) and nitrosative stress (Gursoy-Ozdemir et al., 2000; Gursoy-Ozdemir et al., 2004) and downregulates calpain and caspase-3 in ischemic lesions (Sun et al., 2009). Among the three NOS isoforms, iNOS is most strongly associated with inflammatory responses, and iNOS-produced NO contributes to brain injury (Iadecola et al., 1997). iNOS expression is transcriptionally regulated by NF-κB secondary to moderate inflammatory stimuli such as TNF-α (Trickler et al., 2005; Starke et al., 2014) and IL-1β (Katsuyama et al., 1998), and also by oxidative radicals (Foncea et al., 2000). Contrary to the observed deleterious effects of iNOS-produced NO, NO derived from eNOS is protective in cerebral ischemic injury (Liu et al., 2014). Suppression of eNOS activity produces larger infarcts and more severe reduction in cerebral blood flow (Ito et al., 2010). On the other hand, overexpression of eNOS by flavonoids induces neuroprotection (Li et al., 2006).

**Xenon**

Xenon is one type of anesthetic gas that has gained profound attention because of its potentially neuroprotective properties. As an anesthetic gas, xenon has the advantage of more rapid recovery compared to isoflurane-nitrous oxide anesthesia or propofol anesthesia (Rossaint et al., 2003). As a neuroprotective gas, xenon can improve focal ischemic outcomes (Sheng et al., 2012). In terms of potential mechanism, xenon inhibits the catalytic activity of tissue plasminogen activator (tPA), and thus suppresses tPA-induced hemorrhage and disruption of the blood-brain barrier (David et al., 2010). However, in terms of the impact of xenon on the post-stroke inflammatory responses, evidence is still lacking and further studies would like to yield interesting finding.

**Conclusions**

Collectively, studies in the past two decades have led to a better understanding of the pleiotropic mechanisms of protection afforded by medical gases against cerebral ischemic injury. Inflammation is one of the important mechanisms targeted by various medical gases and it bridges a wide range of signaling pathways. Understanding those mechanisms and their interactions may give rise to novel therapeutic targets and promote clinical translation of medical gas therapy.

**Author contributions**

PYL and XW drafted the manuscript. RAS revised the draft. JC and WFY reviewed and approved the manuscript.

**Conflicts of interest**

None.

**Plagiarism check**

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