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

Pei-ying Li[1, 2], Xin Wang[1], R. Anne Stetler[2], Jun Chen[2], Wei-feng Yu[1, *]

1 Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
2 Pittsburgh Institute of Brain Disorders and Recovery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
*Correspondence to: Wei-feng Yu, yuweifeng@renji.com.
orcid: 0000-0002-6408-2338

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

doi: 10.4103/2045-9912.196906
How to cite this article: Li PY, Wang X, Stetler RA, Chen J, Yu WF (2016) Anti-inflammatory signaling: the point of convergence for medical gases in neuroprotection against ischemic stroke. Med Gas Res 6(4):227-231.
Open access statement: This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

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).

Hyperbaric 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 (Roeckl-Wiedmann et al., 2005), decompression sickness (Bennett et al., 2012). With the capability to relieve cerebral hypoxia, HBO attenuates cerebral vasospasm (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).

Mechanistically, HBO affords protection associated with a variety of beneficial effects, including enhanced neuroplasticity (Efrati et al., 2013), inhibition of matrix metalloproteinase with subsequent attenuation of hemorrhagic transformation (Soejima et al., 2013), modulation of osteopontin expression (Hu et al., 2015) and upregulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/antioxidant defense pathway (Xue et al., 2016). Among these, the impact of HBO on inflammatory signals turns out to be an important part of the HBO-mediated neuroprotection in cerebral ischemia. HBO is linked to a strong downregulation of the activity of p38 mitogen-activated protein kinases (p38 MAPK) (Grimberg-Peters et al., 2016), which is closely related to inflammation. HBO significantly reduced the expression of hypoxia-inducible factor 1alpha (HIF-1a), p53, and Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) extracts from the ischemic tissue in an ischemic wound model, and reduced the expression of endothelial growth factor (Zhang et al., 2008), cyclooxygenase-2, interleukine (IL)-1β and neutrophil infiltration, thus attenuating ischemia-induced inflammation (Cheng et al., 2011).

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-κB) 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 (Cremers 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

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

This paper was double-blinded and stringently reviewed by international expert reviewers.

References

Ansar S, Chatzikonstantinou E, Wistuba-Schier A, Mirau-Weber S, Fatar M, Hennerici MG, Meairs S (2014) Characterization of a new model of thromboembolic stroke in C57 black/6J mice. Transl Stroke Res 5:526-533.

Baxter P, Chen Y, Xu Y, Swanson RA (2014) Mitochondrial dysfunction induced by nuclear poly(ADP-ribose) polymerase-1: a treatable cause of cell death in stroke. Transl Stroke Res 5:136-144.

Bennett MH, Mitchell SJ, Young D, King D (2012) The use of deep tables in the treatment of decompression illness: the Hyperbaric Technicians and Nurses Association 2011 Workshop. Diving Hyperb Med 42:171-180.

Biswas C, Shah N, Muthu M, La P, Fernando AP, Sengupta S, Yang G, Dennery PA (2014) Nuclear heme oxygenase-1 (HO-1) modulates subcellular distribution and activation of Nrf2, impacting metabolic and anti-oxidant defenses. J Biol Chem 289:26882-26894.

Brown CM, Bushnell CD, Samsa GP, Goldstein LB, Colton CA (2015) Chronic systemic immune dysfunction in African-Americans with small vessel-type ischemic stroke. Transl Stroke Res 6:430-436.

Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar TR, McCurry KR, Bauer AJ, Nakao A (2008) Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. Am J Transplant 8:2015-2024.

Cai WW, Zhang MH, Yu YS, Cai JH (2013) Treatment with hydrogen molecule alleviates TNFalpha-induced cell injury in osteoblast. Mol Cell Biochem 373:1-9.

Chen F, Qi Z, Luo Y, Hinchliffe T, Ding G, Xia Y, Ji X (2014) Non-pharmaceutical therapies for stroke: mechanisms and clinical implications. Prog Neurobiol 115:246-269.

Chen H, Sun YP, Li Y, Liu WW, Xiang HG, Fan LY, Sun Q, Xu XY, Cai JM, Ruan CP, Su N, Yan RL, Sun XJ, Wang Q (2010) Hydrogen-rich saline ameliorates the severity of L-arginine-induced acute pancreatitis in rats. Biochem Biophys Res Commun 393:308-313.

Chen S, Yang Q, Chen G, Zhang JH (2015) An update on inflammation in the acute phase of intracerebral hemorrhage. Transl Stroke Res 6:4-8.

Cheng C, Jiang L, Yang Y, Wu H, Huang Z, Sun X (2015) Effect of APOE Gene polymorphism on early cerebral perfusion after aneurysmal subarachnoid hemorrhage. Transl Stroke Res 6:446-450.

Cheng O, Ostrowski RP, Wu B, Liu W, Chen C, Zhang JH (2011) Cyclooxygenase-2 mediates hyperbaric oxygen preconditioning in the rat model of transient global cerebral ischemia. Stroke 42:484-490.

Chung HT, Choi BM, Kwon YG, Kim YM (2008) Interactive relations between nitric oxide (NO) and carbon monoxide (CO): heme oxygenase-1/CO pathway is a key modulator in NO-mediated antiapoptosis and anti-inflammation. Methods Enzymol 441:329-338.

Cremers NA, Lundvig DM, van Dalen SC, Schelbergen RF, van Lent PL, Szarek WA, Regan RF, Carels CE, Wagener FA (2014) Curcumin-induced heme oxygenase-1 expression prevents H_2O_2-induced cell death in wild type and heme oxygenase-2 knockout adipose-derived mesenchymal stem cells. Int J Mol Sci 15:17974-17999.

David HN, Haelewyn B, Risso JJ, Colloc'h N, Abraini JH (2010) Xenon is an inhibitor of tissue-plasminogen activator: adverse and beneficial effects in a rat model of thromboembolic stroke. J Cereb Blood Flow Metab 30:718-728.

Deng J, Lei C, Chen Y, Fang Z, Yang Q, Zhang H, Cai M, Shi L, Dong H, Xiong L (2014) Neuroprotective gases--fantasy or reality for clinical use? Prog Neurobiol 115:210-245.

Ding Z, Tong WC, Lu XX, Peng HP (2014) Hyperbaric oxygen therapy in acute ischemic stroke: a review. Interv Neurol 2:201-211.

Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, Kamiager I, Gal N, Friedman M, Ben-Jacob E, Golan H (2013) Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. PLoS One 8:e53716.

Foncea R, Carvajal C, Almarza C, Leighton F (2000) Endothelial cell oxidative stress and signal transduction. Biol Res 33:89-96.

Gibson CL, Coughlan TC, Murphy SP (2005) Glial nitric oxide and ischemia. Glia 50:417-426.

Ginsberg MD (2016) Expanding the concept of neuroprotection for acute ischemic stroke: The pivotal roles of reperfusion and the collateral circulation. Prog Neurobiol 145-146:46-77

Gonzalez-Moreno EI, Camara-Lemarroy CR, Gonzalez-Gonzalez JG, Gongora-Rivera F (2014) Glycemic variability and acute ischemic stroke: the missing link? Transl Stroke Res 5:638-646.

Grimberg-Peters D, Buren C, Windolf J, Wahlers T, Paunel-Gorgulu A (2016) Hyperbaric oxygen reduces production of reactive oxygen species in neutrophils from polytraumatized patients yielding in the inhibition of p38 MAP kinase and downstream pathways. PLoS One 11:e0161343.

Guresir E, Schuss P, Borger V, Vatter H (2015) Experimental subarachnoid hemorrhage: double cisterna magna injection rat model--assessment of delayed pathological effects of cerebral vasospasm. Transl Stroke Res 6:242-251.

Gursoy-Ozdemir Y, Can A, Dalkara T (2004) Reperfusion-induced oxidative/nitrative injury to neurovascular unit after focal cerebral ischemia. Stroke 35:1449-1453.

Gursoy-Ozdemir Y, Bolay H, Saribas O, Dalkara T (2000) Role of endothelial nitric oxide generation and peroxynitrite formation in reperfusion injury after focal cerebral ischemia. Stroke 31:1974-1980.

Hald ES, Alford PW (2014) Smooth muscle phenotype switching in blast traumatic brain injury-induced cerebral vasospasm. Transl Stroke Res 5:385-393.

Hasegawa Y, Suzuki H, Uekawa K, Kawano T, Kim-Mitsuyama S (2015) Characteristics of cerebrovascular injury in the hyperacute phase after induced severe subarachnoid hemorrhage. Transl Stroke Res 6:458-466.

Hu SL, Huang YX, Hu R, Li F, Feng H (2015) Osteopontin mediates hyperbaric oxygen preconditioning-induced neuroprotection against ischemic stroke. Mol Neurobiol 52:236-243.

Huet O, Pickering RJ, Tikellis C, Latouche C, Long F, Kingwell B, Dickinson B, Chang CJ, Masters S, Mackay F, Cooper ME, de Haan JB (2016) Protective effect of inflammasome activation by hydrogen peroxide in a mouse model of septic shock. Crit Care Med doi:10.1097/CCM.0000000000002070.

Iadecola C (1997) Bright and dark sides of nitric oxide in ischemic brain injury. Trends Neurosci 20:132-139.

Iadecola C, Zhang F, Casey R, Nagayama M, Ross ME (1997) Delayed reduction of ischemic brain injury and neurological deficits in mice lacking the inducible nitric oxide synthase gene. J Neurosci 17:9157-9164.

Ishii T, Itoh K, Takahashi S, Sato H, Yanagawa T, Katoh Y, Bannai S, Yamamoto M (2000) Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. J Biol Chem 275:16023-16029.

Ito Y, Ohkubo T, Asano Y, Hattori K, Shimazu T, Yamazato M, Nagoya H, Kato Y, Araki N (2010) Nitric oxide production during cerebral ischemia and reperfusion in eNOS- and nNOS-knockout mice. Curr Neurovasc Res 7:23-31.

Katsuyama K, Shichiri M, Marumo F, Hirata Y (1998) NO inhibits cytokine-induced iNOS expression and NF-kappaB activation by interfering with phosphorylation and degradation of IkappaB-alpha. Arterioscler Thromb Vasc Biol 18:1796-1802.

Kawasaki H, Guan J, Tamama K (2010) Hydrogen gas treatment prolongs replicative lifespan of bone marrow multipotential stromal cells in vitro while preserving differentiation and paracrine potentials. Biochem Biophys Res Commun 397:608-613.

Khan M, Sekhon B, Giri S, Jatana M, Gilg AG, Ayasolla K, Elango C, Singh AK, Singh I (2005) S-Nitrosoglutathione reduces inflammation and protects brain against focal cerebral ischemia in a rat model of experimental stroke. J Cereb Blood Flow Metab 25:177-192.

Lee YS, Chio CC, Chang CP, Wang LC, Chiang PM, Niu KC, Tsai KJ (2013) Long course hyperbaric oxygen stimulates neurogenesis and attenuates inflammation after ischemic stroke. Mediators Inflamm 2013:512978.

Li GM, Ji MH, Sun XJ, Zeng QT, Tian M, Fan YX, Li WY, Li N, Yang JJ (2013) Effects of hydrogen-rich saline treatment on polymicrobial sepsis. J Surg Res 181:279-286.

Li R, Guo M, Zhang G, Xu X, Li Q (2006) Nicotiflorin reduces cerebral ischemic damage and upregulates endothelial nitric oxide synthase in primarily cultured rat cerebral blood vessel endothelial cells. J Ethnopharmacol 107:143-150.

Liu J, Wang Y, Akamatsu Y, Lee CC, Stetler RA, Lawton MT, Yang GY (2014) Vascular remodeling after ischemic stroke: mechanisms and therapeutic potentials. Prog Neurobiol 115:138-156.

Ma Y, Wang J, Wang Y, Yang GY (2016) The biphasic function of microglia in ischemic stroke. Prog Neurobiol.

Nathan C (1992) Nitric oxide as a secretory product of mammalian cells. FASEB J 6:3051-3064.

Niwa M, Inao S, Takayasu M, Kawai T, Kajita Y, Nihashi T, Kabeya R, Sugimoto T, Yoshida J (2001) Time course of expression of three nitric oxide synthase isoforms after transient middle cerebral artery occlusion in rats. Neurol Med Chir 41:63-72.

Oh S, Choi SC (2015) Acute carbon monoxide poisoning and delayed neurological sequelae: a potential neuroprotection bundle therapy. Neural Regen Res 10:36-38

Ohta S (2014) Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. Pharmacol Ther 144:1-11.

Patil K, Bellner L, Cullaro G, Gotlinger KH, Dunn MW, Schwartzman ML (2008) Heme oxygenase-1 induction attenuates corneal inflammation and accelerates wound healing after epithelial injury. Invest Ophthalmol Vis Sci 49:3379-3386.

Pennypacker KR (2014) Targeting the peripheral inflammatory response to stroke: role of the spleen. Transl Stroke Res 5:635-637.

Poittevin M, Lozeron P, Hilal R, Levy BI, Merkulova-Rainon T, Kubis N (2014) Smooth muscle cell phenotypic switching in stroke. Transl Stroke Res 5:377-384.

Roeckl-Wiedmann I, Bennett M, Kranke P (2005) Systematic review of hyperbaric oxygen in the management of chronic wounds. Br J Surg 92:24-32.

Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, Giunta F, Del Turco M, Erdmann W, Tenbrinck R, Hammerle AF, Nagele P; Xenon Study Group (2003) Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology 98:6-13.

Schallner N, Pandit R, LeBlanc R 3rd, Thomas AJ, Ogilvy CS, Zuckerbraun BS, Gallo D, Otterbein LE, Hanafy KA (2015) Microglia regulate blood clearance in subarachnoid hemorrhage by heme oxygenase-1. J Clin Invest 125:2609-2625.

Seifert HA, Pennypacker KR (2014) Molecular and cellular immune responses to ischemic brain injury. Transl Stroke Res 5:543-553.

Sheng SP, Lei B, James ML, Lascola CD, Venkatraman TN, Jung JY, Maze M, Franks NP, Pearlstein RD, Sheng H, Warner DS (2012) Xenon neuroprotection in experimental stroke: interactions with hypothermia and intracerebral hemorrhage. Anesthesiology 117:1262-1275.

Shimamura N, Ohkuma H (2014) Phenotypic transformation of smooth muscle in vasospasm after aneurysmal subarachnoid hemorrhage. Transl Stroke Res 5:357-364.

Soejima Y, Hu Q, Krafft PR, Fujii M, Tang J, Zhang JH (2013) Hyperbaric oxygen preconditioning attenuates hyperglycemia-enhanced hemorrhagic transformation by inhibiting matrix metalloproteinases in focal cerebral ischemia in rats. Exp Neurol 247:737-743.

Starke RM, Raper DM, Ding D, Chalouhi N, Owens GK, Hasan DM, Medel R, Dumont AS (2014) Tumor necrosis factor-alpha modulates cerebral aneurysm formation and rupture. Transl Stroke Res 5:269-277.

Stetler RA, Leak RK, Gan Y, Li P, Zhang F, Hu X, Jing Z, Chen J, Zigmond MJ, Gao Y (2014) Preconditioning provides neuroprotection in models of CNS disease: paradigms and clinical significance. Prog Neurobiol 114:58-83.

Sun M, Zhao Y, Gu Y, Xu C (2009) Inhibition of nNOS reduces ischemic cell death through down-regulating calpain and caspase-3 after experimental stroke. Neurochem Int 54:339-346.

Suzuki M, Tabuchi M, Ikeda M, Tomita T (2002) Concurrent formation of peroxynitrite with the expression of inducible nitric oxide synthase in the brain during middle cerebral artery occlusion and reperfusion in rats. Brain Res 951:113-120.

Trickler WJ, Mayhan WG, Miller DW (2005) Brain microvessel endothelial cell responses to tumor necrosis factor-alpha involve a nuclear factor kappa B (NF-kappaB) signal transduction pathway. Brain Res 1048:24-31.

Wang B, Cao W, Biswal S, Dore S (2011) Carbon monoxide-activated Nrf2 pathway leads to protection against permanent focal cerebral ischemia. Stroke 42:2605-2610.

Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, Orme JF, Jr., Thomas FO, Morris AH (2002) Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 347:1057-1067.

Wu L, Walas S, Leung W, Sykes DB, Wu J, Lo EH, Lok J (2015) Neuregulin1-beta decreases IL-1beta-induced neutrophil adhesion to human brain microvascular endothelial cells. Transl Stroke Res 6:116-124.

Xiong XY, Yang QW (2015) Rethinking the roles of inflammation in the intracerebral hemorrhage. Transl Stroke Res 6:339-341.

Xiong XY, Wang J, Qian ZM, Yang QW (2014) Iron and intracerebral hemorrhage: from mechanism to translation. Transl Stroke Res 5:429-441.

Xue F, Huang JW, Ding PY, Zang HG, Kou ZJ, Li T, Fan J, Peng ZW, Yan WJ (2016) Nrf2/antioxidant defense pathway is involved in the neuroprotective effects of Sirt1 against focal cerebral ischemia in rats after hyperbaric oxygen preconditioning. Behav Brain Res 309:1-8.

Yu HM, Xu J, Li C, Zhou C, Zhang F, Han D, Zhang GY (2008) Coupling between neuronal nitric oxide synthase and glutamate receptor 6-mediated c-Jun N-terminal kinase signaling pathway via S-nitrosylation contributes to ischemia neuronal death. Neuroscience 155:1120-1132.

Zhang Q, Chang Q, Cox RA, Gong X, Gould LJ (2008) Hyperbaric oxygen attenuates apoptosis and decreases inflammation in an ischemic wound model. J Invest Dermatol 128:2102-2112.

Zhao H, Garton T, Keep RF, Hua Y, Xi G (2015) Microglia/macrophage polarization after experimental intracerebral hemorrhage. Transl Stroke Res 6:407-409.

Zhao X, Aronowski J (2013) Nrf2 to pre-condition the brain against injury caused by products of hemolysis after ICH. Transl Stroke Res 4:71-75.

Zhou L, Zhu DY (2009) Neuronal nitric oxide synthase: structure, subcellular localization, regulation, and clinical implications. Nitric Oxide 20:223-230.