Anti-oxidative aspect of inhaled anesthetic gases against acute brain injury

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Abstract

Acute brain injury is a critical and emergent condition in clinical settings, which needs to be addressed urgently. Commonly acute brain injuries include traumatic brain injury, ischemic and hemorrhagic strokes. Oxidative stress is a key contributor to the subsequent injuries and impedes the reparative process after acute brain injury; therefore, facilitating an anti-oxidative approach is important in the care of those diseases. Readiness to deliver and permeability to blood brain barrier are essential for the use of this purpose. Inhaled anesthetic gases are a group of such agents. In this article, we discuss the anti-oxidative roles of anesthetic gases against acute brain injury.

Key words: isoflurane; nuclear factor (erythroid-derived 2)-like 2; pre-conditioning; post-conditioning; sevoflurane; stroke; traumatic brain injury; xenon

INTRODUCTION

Oxidative stress is common in the brain following acute injuries, such as trauma, ischemic or hemorrhagic strokes (Chong et al., 2005; Rodrigo et al., 2013; Seifert and Pennypacker, 2014; Xiong et al., 2014; Hasegawa et al., 2015; Schlunk and Greenberg, 2015; Suzuki, 2015). The primary targets of reactive oxygen species (ROS) or reactive nitrogen species (RNS) following acute brain injury are macromolecules, including proteins, fatty acids and lipids, and deoxyribonucleic acids. The secondary effects of ROS and RNS are multiple; for example, they trigger apoptosis and neuroinflammation (Rodrigo et al., 2013; Ahmad et al., 2014; Fayaz et al., 2014; Seifert and Pennypacker, 2014; Chen et al., 2015a, b; Xiong and Yang, 2015; Zhao et al., 2015). The brain is rich in lipids and vulnerable to oxidative stress; therefore, anti-oxidative approach has priority in protecting the brain (Chong et al., 2005; Rodrigo et al., 2013).

ANTI-OXIDATIVE SYSTEMS

Biological entities have built-in anti-oxidative systems, and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a key member in the systems. Nrf2 is a master transcription factor that controls the expression of a battery of anti-oxidative enzymes (van Muiswinkel and Kuiperij, 2005; Zhang et al., 2013). Under physiological conditions, Nrf2 is sequestered in the cellular cytosol and quickly degraded by the S26 proteasomes after its synthesis. The regulation of Nrf2 degradation has two arms, one is by Kelch-like ECH associated protein 1 (Keap1) and Cullin3 (Cul3)-

related E3 ligase, and the other is by glycogen synthase kinase 3 (GSK3β) and another E3 ligase known as beta-transducin repeat-containing protein. Following oxidative stress, Keap1 or GSK3β undergoes modification and loses the ability to bind Nrf2; free Nrf2 then translocates to the nucleus and upregulates the expression of downstream anti-oxidative genes. Furthermore, the activity of Nrf2 can be regulated *via* phosphorylation by protein kinases, such as protein kinase B and C (Cross et al., 1995; Zhang et al., 2013), and the phosphorylation of Nrf2 affects its binding to Keap1 and its nuclear transportation (Zhang et al., 2013).

ANTI-OXIDATIVE ENZYMES INDUCED BY INHALED ANESTHETIC GASES

The downstream genes of Nrf2 include four groups of anti-oxidative enzymes (van Muiswinkel and Kuiperij, 2005; Zhang et al., 2013). (1) Detoxifying enzymes, including heme oxygenase 1 (HO-1) and NAD(P)H: quinone oxidoreductase 1. (2) Glutathione group, such as glutathione synthetases and glutathione peroxidases. (3) Thioredoxin enzyme group, including thioredoxins, thioredoxin reductases, peroxiredoxins, and sulfiredoxin. (4) Transferase group, such as glutathione S-transferase, sulfotransferase. These enzymes can be induced on purpose by using Nrf2 activators, including some inhaled anesthetic gases (Hoetzel and Schmidt, 2010; Zhao et al., 2013; Lee et al., 2015).

PROTECTIVE EFFECT OF INHALED ANESTHETIC GASES

The inhaled anesthetic gases that are widely applied in clinic settings and in experimental studies include isoflurane, sevoflurane and xenon, especially isoflurane (Zhang et al., 2012, 2014b; Hu et al., 2014; Sehba, 2014; Chen et al., 2015a; Cheng et al., 2015; Schlunk et al., 2015; Zuloaga et al., 2015). Importantly, isoflurane has been reported to reduce the brain injury induced by ischemic stroke (Bickler and Fahlman, 2006; Li and Zuo, 2009; Bedirli et al., 2012; Yin et al., 2014; Sosunov et al., 2015) and hemorrhagic stroke (Gigante et al., 2011; Altay et al., 2012). Sevoflurane protects the brain against ischemic stroke (Engelhard et al., 2003; Wang et al., 2011, 2016; Yu et al., 2011; Bedirli et al., 2012; Li et al., 2014), and hemorrhagic stroke (Karwacki et al., 2005; Lee et al., 2015). The research on desflurane is limited; however, its protection against ischemia has been reported (Haelewyn et al., 2003). Xenon protects the brain against traumatic brain injury (TBI) (Harris et al., 2013) and ischemic injury (Dingley et al., 2006; Hobbs et al., 2008; Esencan et al., 2013; Sabir et al., 2014; Liu et al., 2016).

The inhaled anesthetic gases can be used as either a pre-conditioning approach or a post-conditioning one. Pre-conditioning has demonstrated protective effects against TBI (Harris et al., 2013; Deng et al., 2014; Khan et al., 2015; Shu et al., 2016), ischemic stroke (Dingley et al., 2006; Wang et al., 2011, 2016; Yu et al., 2011; Liu et al., 2013; Shi et al., 2013), and hemorrhagic stroke (Gigante et al., 2011; Sheng et al., 2012). Post-conditioning is a relative new concept and it has been reported in ischemic stroke (Li et al., 2014; Yin et al., 2014; Lee et al., 2015; Liu et al., 2016).

ANTI-OXIDATIVE MECHANISMS OF INHALED ANESTHETIC GASES

The anti-oxidative mechanisms of these inhaled anesthetic gases are not fully understood, especially the ways they activate Nrf2 pathway. Although there are no reports showing that these gases inhibit Keap1, it has been reported that isoflurane, sevoflurane, and desflurane inhibit GSK3β activity and reduce neuronal injury after oxygen-glucose deprivation (Lin et al., 2011). It seems that activating protein kinases is an important approach for the gases to activate Nrf2 pathway. Both isoflurane and sevoflurane have been reported to activate phosphoinositide 3 kinase (PI3K) and protein kinase B (Akt) (Bickler and Fahlman, 2006; Ye et al., 2012; Zhang et al., 2014a), and sevoflurane can activate protein kinase C (Lee et al., 2015). Xenon may activate Nrf2 pathway by phosphorylating Akt and extracellular signal-regulated kinases (Liu et al., 2016).

CLINICAL PROSPECT

It is certain that these inhaled anesthetic gases offer anti-oxidative and neuroprotective effects against TBI and strokes. There are several advantages to use anesthetic gases in clinical settings. They have been used for many years in clinical settings. Moreover, they are safe, fat-soluble with high permeability to blood brain barrier, which are critical for delivery to the brain. In addition, they are routinely given with oxygen, making them preferable and convenient for clinical use, especially in emergent conditions and in operation room. However, several aspects need to be clarified for clinical translation, such as the optimal dose and route for delivery, their protective mechanisms, and the machineries by which they activate Nrf2 pathway and upregulate anti-oxidative enzymes.

References

Ahmad M, Dar NJ, Bhat ZS, Hussain A, Shah A, Liu H, Graham SH (2014) Inflammation in ischemic stroke: mechanisms, consequences and possible drug targets. CNS Neurol Disord Drug Targets 13:1378-1396.

Altay O, Suzuki H, Hasegawa Y, Caner B, Krafft PR, Fujii M, Tang J, Zhang JH (2012) Isoflurane attenuates blood-brain barrier disruption in ipsilateral hemisphere after subarachnoid hemorrhage in mice. Stroke 43:2513-2516.

Bedirli N, Bagriacik EU, Emmez H, Yilmaz G, Unal Y, Ozkose Z (2012) Sevoflurane and isoflurane preconditioning provides neuroprotection by inhibition of apoptosis-related mRNA expression in a rat model of focal cerebral ischemia. J Neurosurg Anesthesiol 24:336-344.

Bickler PE, Fahlman CS (2006) The inhaled anesthetic, isoflurane, enhances Ca^{2+}-dependent survival signaling in cortical neurons and modulates MAP kinases, apoptosis proteins and transcription factors during hypoxia. Anesth Analg 103:419-429.

Chen F, Du Y, Esposito E, Liu Y, Guo S, Wang X, Lo EH, Xing C, Ji X (2015a) Effects of focal cerebral ischemia on exosomal versus serum miR126. Transl Stroke Res 6:478-484.

Chen S, Yang Q, Chen G, Zhang JH (2015b) 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.

Chong ZZ, Li F, Maiese K (2005) Oxidative stress in the brain: Novel cellular targets that govern survival during neurodegenerative disease. Prog Neurobiol 75:207-246.

Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 378.

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.

Dingley J, Tooley J, Porter H, Thoresen M (2006) Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. Stroke 37:501-506.

Engelhard K, Werner C, Hoffman WE, Matthes B, Blobner M, Kochs E (2003) The effect of sevoflurane and propofol on cerebral neurotransmitter concentrations during cerebral ischemia in rats. Anesth Analg 97:1155-1161.

Esencan E, Yuksel S, Tosun YB, Robinot A, Solaroglu I, Zhang JH (2013) XENON in medical area: emphasis on neuroprotection in hypoxia and anesthesia. Med Gas Res 3:4.

Fayaz SM, Suvanish Kumar VS, Rajanikant GK (2014) Necroptosis: who knew there were so many interesting ways to die? CNS Neurol Disord Drug Targets 13:42-51.

Gigante PR, Appelboom G, Hwang BY, Haque RM, Yeh ML, Ducruet AF, Kellner CP, Gorski J, Keesecker SE, Connolly ES, Jr. (2011) Isoflurane preconditioning affords functional neuroprotection in a murine model of intracerebral hemorrhage. Acta Neurochir Suppl 111:141-144.

Haelewyn B, Yvon A, Hanouz JL, MacKenzie ET, Ducouret P, Gerard JL, Roussel S (2003) Desflurane affords greater protection than halothane against focal cerebral ischaemia in the rat. Br J Anaesth 91:390-396.

Harris K, Armstrong SP, Campos-Pires R, Kiru L, Franks NP, Dickinson R (2013) Neuroprotection against traumatic brain injury by xenon, but not argon, is mediated by inhibition at the N-methyl-D-aspartate receptor glycine site. Anesthesiology 119:1137-1148.

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.

Hobbs C, Thoresen M, Tucker A, Aquilina K, Chakkarapani E, Dingley J (2008) Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. Stroke 39:1307-1313.

Hoetzel A, Schmidt R (2010) Regulatory role of anesthetics on heme oxygenase-1. Curr Drug Targets 11:1495-1503.

Hu R, Huang D, Tong J, Liao Q, Hu Z, Ouyang W (2014) Aspartic acid in the hippocampus: a biomarker for postoperative cognitive dysfunction. Neural Regen Res 9:143-152.

Karwacki Z, Kowianski P, Dziewiatkowski J, Domaradzka-Pytel B, Ludkiewicz B, Wojcik S, Narkiewicz O, Morys J (2005) The influence of sevoflurane on the reactivity of astrocytes in the course of the experimental intracerebral haemorrhage in rat. J Physiol Pharmacol 56:455-469.

Khan MB, Hoda MN, Vaibhav K, Giri S, Wang P, Waller JL, Ergul A, Dhandapani KM, Fagan SC, Hess DC (2015) Remote ischemic postconditioning: harnessing endogenous protection in a murine model of vascular cognitive impairment. Transl Stroke Res 6:69-77.

Lee H, Park YH, Jeon YT, Hwang JW, Lim YJ, Kim E, Park SY, Park HP (2015) Sevoflurane post-conditioning increases nuclear factor erythroid 2-related factor and haemoxygenase-1 expression via protein kinase C pathway in a rat model of transient global cerebral ischaemia. Br J Anaesth 114:307-318.

Li B, Sun J, Lv G, Yu Y, Wang G, Xie K, Jiao Y, Yu Y (2014) Sevoflurane postconditioning attenuates cerebral ischemia-reperfusion injury via protein kinase B/nuclear factor-erythroid 2-related factor 2 pathway activation. Int J Dev Neurosci 38:79-86.

Li L, Zuo Z (2009) Isoflurane preconditioning improves short-term and long-term neurological outcome after focal brain ischemia in adult rats. Neuroscience 164:497-506.

Lin D, Li G, Zuo Z (2011) Volatile anesthetic post-treatment induces protection via inhibition of glycogen synthase kinase 3 beta in human neuron-like cells. Neuroscience 179:73-79.

Liu S, Yang Y, Jin M, Hou S, Dong X, Lu J, Cheng W (2016) Xenon-delayed postconditioning attenuates spinal cord ischemia/reperfusion injury through activation AKT and ERK signaling pathways in rats. J Neurol Sci 368:277-284.

Liu W, Liu Y, Chen H, Liu K, Tao H, Sun X (2013) Xenon preconditioning: molecular mechanisms and biological effects. Med Gas Res 3:3.

Rodrigo R, Fernandez-Gajardo R, Gutierrez R, Matamala JM, Carrasco R, Miranda-Merchak A, Feuerhake W (2013) Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. CNS Neurol Disord Drug Targets 12:698-714.

Sabir H, Walloe L, Dingley J, Smit E, Liu X, Thoresen M (2014) Combined treatment of xenon and hypothermia in newborn rats--additive or synergistic effect? PLoS One 9:e109845.

Schlunk F, Greenberg SM (2015) The pathophysiology of intracerebral hemorrhage formation and expansion. Transl Stroke Res 6:257-263.

Schlunk F, Schulz E, Lauer A, Yigitkanli K, Pfeilschifter W, Steinmetz H, Lo EH, Foerch C (2015) Warfarin pretreatment reduces cell death and MMP-9 activity in experimental intracerebral hemorrhage. Translational stroke research 6:133-139.

Sehba FA (2014) Rat endovascular perforation model. Transl Stroke Res 5:660-668.

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.

Shi H, Sun BL, Zhang J, Lu S, Zhang P, Wang H, Yu Q, Stetler RA, Vosler PS, Chen J, Gao Y (2013) miR-15b suppression of Bcl-2 contributes to cerebral ischemic injury and is reversed by sevoflurane preconditioning. CNS Neurol Disord Drug Targets 12:381-391.

Shu L, Wang C, Wang J, Zhang Y, Zhang X, Yang Y, Zhuo J, Liu J (2016) The neuroprotection of hypoxic preconditioning on rat brain against traumatic brain injury by up-regulated transcription factor Nrf2 and HO-1 expression. Neurosci Lett 611:74-80.

Sosunov SA, Ameer X, Niatsetskaya ZV, Utkina-Sosunova I, Ratner VI, Ten VS (2015) Isoflurane anesthesia initiated at the onset of reperfusion attenuates oxidative and hypoxic-ischemic brain injury. PLoS One 10.

Suzuki H (2015) What is early brain injury? Transl Stroke Res 6:1-3.

van Muiswinkel FL, Kuiperij HB (2005) The Nrf2-ARE Signalling pathway: promising drug target to combat oxidative stress in neurodegenerative disorders. Curr Drug Targets CNS Neurol Disord 4:267-281.

Wang H, Shi H, Yu Q, Chen J, Zhang F, Gao Y (2016) Sevoflurane preconditioning confers neuroprotection via anti-apoptosis effects. Acta Neurochir Suppl 121:55-61.

Wang H, Lu S, Yu Q, Liang W, Gao H, Li P, Gan Y, Chen J, Gao Y (2011) Sevoflurane preconditioning confers neuroprotection via anti-inflammatory effects. Front Biosci (Elite Ed) 3:604-615.

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.

Ye Z, Guo Q, Xia P, Wang N, Wang E, Yuan Y (2012) Sevoflurane postconditioning involves an up-regulation of HIF-1α and HO-1 expression via PI3K/Akt pathway in a rat model of focal cerebral ischemia. Brain Res 1463:63-74.

Yin JB, Li H, Feng CZ, Zuo ZY (2014) Inhibition of brain ischemia-caused notch activation in microglia may contribute to isoflurane postconditioning-induced neuroprotection in male rats. CNS Neurol Disord Drug Targets 13:718-732.

Yu Q, Chu M, Wang H, Lu S, Gao H, Li P, Gan Y, Shi H, Liang W, Chen J, Gao Y (2011) Sevoflurane preconditioning protects blood-brain-barrier against brain ischemia. Front Biosci (Elite Ed) 3:978-988.

Zhang F, Wang S, Zhang M, Weng Z, Li P, Gan Y, Zhang L, Cao G, Gao Y, Leak RK, Sporn MB, Chen J (2012) Pharmacological induction of heme oxygenase-1 by a triterpenoid protects neurons against ischemic injury. Stroke 43:1390-1397.

Zhang L, Zhang J, Dong Y, Swain CA, Zhang Y, Xie Z (2014a) The potential dual effects of sevoflurane on AKT/GSK3β signaling pathway. Med Gas Res 4:1-9.

Zhang M, Wang S, Mao L, Leak RK, Shi Y, Zhang W, Hu X, Sun B, Cao G, Gao Y, Xu Y, Chen J, Zhang F (2014b) Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. J Neurosci 34:1903-1915.

Zhang MJ, An CR, Gao YQ, Leak RK, Chen J, Zhang F (2013) Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. Prog Neurobiol 100:30-47.

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 HL, Yoshida A, Xiao W, Ologunde R, O'Dea KP, Takata M, Tralau-Stewart C, George AJ, Ma DQ (2013) Xenon treatment attenuates early renal allograft injury associated with prolonged hypothermic storage in rats. FASEB J 27:4076-4088.

Zuloaga KL, Zhang W, Yeiser LA, Stewart B, Kukino A, Nie X, Roese NE, Grafe MR, Pike MM, Raber J, Alkayed NJ (2015) Neurobehavioral and imaging correlates of hippocampal atrophy in a mouse model of vascular cognitive impairment. Transl Stroke Res 6:390-398.