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

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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 Fahman, 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 (Karwaki 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 Fahman, 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.

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**Author contributions**

TY, YS, and FZ collected the references and drafted the manuscript. All authors read and approved the final manuscript.
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