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Carbon monoxide and anesthesia-induced neurotoxicity☆

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ABSTRACT

The majority of commonly used anesthetic agents induce widespread neuronal degeneration in the developing mammalian brain. Downstream, the process appears to involve activation of the oxidative stress-associated mitochondrial apoptosis pathway. Targeting this pathway could result in prevention of anesthetic toxicity in the immature brain. Carbon monoxide (CO) is a gas that exerts biological activity in the developing brain and low dose exposures have the potential to provide neuroprotection. In recent work, low concentration CO exposures limited isoflurane-induced neuronal apoptosis in a dose-dependent manner in newborn mice and modulated oxidative stress within forebrain mitochondria. Because infants and children are routinely exposed to low levels of CO during low-flow general endotracheal anesthesia, such anti-oxidant and pro-survival cellular effects are clinically relevant. Here we provide an overview of anesthesia-related CO exposure, discuss the biological activity of low concentration CO, detail the effects of CO in the brain during development, and provide evidence for CO-mediated inhibition of anesthesia-induced neurotoxicity.

1. Introduction

The majority of commonly used anesthetic agents induce widespread neuronal degeneration in the developing mammalian brain, resulting in behavioral impairments and cognitive deficits later in life (Jevtovic-Todorovic et al., 2003; Stefovska et al., 2008; Istaphanous and Loepke, 2009; Brambrink et al., 2010; Istaphanous et al., 2011). This toxicological effect has been demonstrated in a variety of newborn animal models including non-human primates (Brambrink et al., 2010; Olney et al., 2004; Rizzi et al., 2010). Although a causal relationship has yet to be established in humans, several retrospective studies have demonstrated an association between anesthesia exposure in young children and subsequent defects in learning and scholastic performance (Wilder et al., 2009; DiMaggio et al., 2009; Flick et al., 2011; Psaty et al., 2015). The exact mechanisms of anesthesia-induced neurotoxicity have not been fully elucidated, however, the downstream process appears to involve activation of the oxidative stress-associated mitochondrial apoptosis pathway (Olney et al., 2004; Yon et al., 2005; Bai et al., 2013; Boscolo et al., 2013; Zhang et al., 2010). Thus, targeting this pathway is a strategy that could lead to development of novel therapeutic agents which will prevent or limit anesthetic toxicity in the immature brain.

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas that is biologically active in many different tissues and organs (Iqbal et al., 2012; Kao and Nañagas, 2005). In the brain, CO has the potential to cause neurotoxicity or provide neuroprotection depending on the context, duration, and concentration of exposure. Overt toxicity is the most widely recognized effect of CO due to the well-characterized tissue hypoxia that results following exposure to high concentrations (Kao and Nañagas, 2005). However, at low concentrations, CO acts as a signaling molecule, affecting several different cellular pathways in a more intricate and complex manner (Kapetanaki et al., 2009; Ignarro et al., 1982; Furchgott and Jothianandan, 1991; Morita et al., 1997; Kim et al., 2006; Otterbein et al., 2000; Kim et al., 2005a; Kim et al., 2005b; Rhodes et al., 2009; Lee et al., 2011; Chiang et al., 2013). These sub-toxic concentrations have been shown to confer cytoprotection through an array of mechanisms (Kapetanaki et al., 2009; Ignarro et al., 1982; Furchgott and Jothianandan, 1991; Morita et al., 1997; Kim et al., 2006; Otterbein et al., 2000; Kim et al., 2005a; Kim et al., 2005b; Rhodes et al., 2009; Lee et al., 2011; Chiang et al., 2013). As a result, low dose CO is currently being explored as a novel treatment for a variety of diseases processes.

Recently, we demonstrated that exposure to low concentration CO limited isoflurane-induced neuronal apoptosis in a dose-dependent manner and modulated oxidative stress within forebrain mitochondria

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in a newborn mouse model of anesthesia-induced neurotoxicity (Cheng and Levy, 2014; Cheng et al., 2015). Because infants and children are routinely exposed to low levels of CO during low-flow general endotracheal anesthesia, investigation of CO as a potential therapy to offset the deleterious effects of anesthetics in the developing brain has clinical relevance. Here we provide an overview of anesthesia-related CO exposure, discuss the biological activity of low concentration CO, detail the effects of CO in the brain during development, and provide evidence for CO-mediated inhibition of anesthesia-induced neurotoxicity.

2. CO exposure during low-flow general endotracheal anesthesia

Low-flow anesthesia (LFA) is a commonly used, cost-saving paradigm which permits rebreathing in order to conserve volatile anesthetic agents (Baum and Aitkenhead, 1995). Although there is no widely accepted definition, LFA generally refers to an anesthetic technique involving delivery of fresh gas at 1 l per minute or less in adults (Nunn, 2008). In children, a low-flow approach results in rebreathing when the rate of minute ventilation exceeds the rate of fresh gas flow (FGF) (Levy et al., 2010; Nasr et al., 2010). Exposure to CO routinely occurs during LFA and the extent of exposure inversely correlates with the FGF-to-minute ventilation ratio (Levy et al., 2010; Tang et al., 2001). Infants and children have been shown to inspire up to 20 ppm (ppm) CO during a low-flow general endotracheal anesthetic when the rate of FGF was set below the rate of minute ventilation (Levy et al., 2010; Nasr et al., 2010). CO manifests in the anesthesia breathing system in this setting from endogenous patient sources but may also be generated exogenously within the circuit (Coppens et al., 2006; Woehlck, 2001). Exogenous CO is produced when volatile anesthetic agents are degraded by conventional carbon dioxide absorbents while endogenously formed CO is present in exhaled breath (Coppens et al., 2006; Woehlck, 2001; Baxter et al., 1998).

Degradation occurs with all of the volatile anesthetics currently in use today and is catalyzed by the base of conventional absorbents (Baxter et al., 1998; Fang et al., 1995; Keijzer et al., 2005; Woehlck et al., 2001). Strong alkali hydroxides, such as potassium and sodium hydroxide, are the chemical components that are primarily responsible (Neumann et al., 1999). Water content is another key factor that determines the degree of anesthetic degradation and the amount of CO formed is inversely proportional to the amount of water in the absorbent (Fang et al., 1995; Baxter and Kharasch, 1997). Other important variables that influence anesthetic degradation include the absorbent temperature, type of volatile agent, anesthetic concentration, and patient carbon dioxide production (Fang et al., 1995; Fan et al., 2008).

In order to limit chemical breakdown of volatile anesthetics and CO formation, the Anesthesia Patient Safety Foundation (APSF) recommends using absorbents that lack strong alkali hydroxides or avoiding conventional absorbent desiccation (Olympio, 2016; Murray et al., 1999). Although adherence to the APSF guidelines reduces the risk of generating overtly toxic levels of CO, it does not prevent exposure to low concentrations of CO. One reason for this is that even fully hydrated conventional absorbents are capable of degrading volatile agents (Fan et al., 2008). For example, completely hydrated soda lime has been shown to generate up to 23 ppm CO during a 2-h desflurane anesthetic (Fan et al., 2008). Although the amount of CO produced from hydrated absorbent is markedly less than that generated by dried absorbent, CO formation still occurs and varies based on the rate of FGF (Fan et al., 2008). This is because smaller volumes of fresh gas limit the dilution of CO within the breathing circuit, thus, lower rates of FGF result in higher CO concentrations (Fan et al., 2008).

Another source of CO exposure during LFA is patient-derived, endogenously generated CO (Woehlck, 2001). CO is formed naturally within the liver, spleen, and kidney, and within the central nervous system and reticuloendothelial system during heme catabolism (Hayashi et al., 2004). Following its generation, CO diffuses into the circulation, binds to hemoglobin, and is excreted by the lungs as a component of exhaled breath (Hayashi et al., 2004). During LFA, exhaled CO is not scavenged or removed from the closed anesthesia breathing circuit (Woehlck, 2001). As a consequence, patients rebreathe exhaled CO, resulting in an active exposure (Woehlck, 2001).

Therefore, patients are commonly exposed to CO during low-flow general endotracheal anesthesia. In the current era, the majority of anesthesia-related CO exposures are sub-toxic (below the threshold for tissue hypoxia). Although the significance of such exposures is not well understood, it is known that CO acts as a signaling molecule at these levels. Low concentration CO exerts biological activity in many organs and tissues including the immature brain (Levy, 2015). Thus, CO exposure during LFA could have implications for infants and children. In the next few sections we will review the cellular effects of low concentration CO and detail the known neurodevelopmental consequences of such exposures.

3. Biological activity of CO

Following inhalation, CO readily diffuses across the alveolar capillary membrane to bind to hemoglobin, forming carboxyhemoglobin (COHb) (Smithline et al., 2003). The affinity of hemoglobin is 240 times greater for CO than for oxygen and high COHb levels can interfere with oxygen binding and dissociation (Hauck and Neuberger, 1984; Gorman et al., 2003). This leads to impaired tissue oxygen delivery by shifting the oxygen-hemoglobin dissociation curve to the left (Gorman et al., 2003). High concentrations of CO can also directly interfere with aerobic cellular energy production by binding to hemoproteins within the cytosol and mitochondria (Brown and Piantadosi, 1990; Iheagwara et al., 1772). Thus, toxic CO exposures result in tissue and cellular hypoxia and clinically detectable signs and symptoms manifest when COHb levels exceed 20% (Table 1) (Kao and Nañagas, 2005).

The amount of COHb formed and the manifestation of toxic effects relate to the concentration and the duration of CO exposure (Table 1) (Winter and Miller, 1976; Raub, 1999). This time-weighted relationship dictates the degree of toxicity, or lack thereof (Winter and Miller, 1976). For example, exposure to between 70 and 120 ppm CO for approximately 4 h is considered a low concentration exposure and results in COHb levels between 10 and 20% (Winter and Miller, 1976; Raub and Benignus, 2002; Tomaszewski, 2002). Such an exposure is usually asymptomatic, does not cause tissue hypoxia, and is not life threatening (Winter and Miller, 1976; Raub and Benignus, 2002; Tomaszewski, 2002). Lack of detectable signs and symptoms defines this type of CO exposure as sub-clinical and sub-toxic (Winter and Miller, 1976). On the other hand, exposure to CO concentrations in excess of 200 ppm results in COHb levels of approximately 30% and readily causes headache, dizziness, and impaired judgment (Winter and Miller, 1976). While, inspiring >800 ppm CO is considered a high concentration exposure and results in COHb levels that exceed 60% and can rapidly lead to seizures, coma, and death (Winter and Miller, 1976).

In contrast to the hypoxia-inducing, toxic concentrations, low dose CO exerts complex biological activity in a variety of cells and tissues even at nanomolar concentrations (Kapetanaki et al., 2009). These gasotransmitter properties were first uncovered following discovery of the ability of CO to weakly stimulate soluble guanylate cyclase to generate cyclic guanosine 3′,5′-monophosphate (cGMP) (Ignarro et al., 1982; Furchgott and Jothianandan, 1991; Morita et al., 1997). Since its identification as a signaling molecule, CO has been shown to modulate several p38 mitogen-activated protein kinase (MAPK)-related signaling pathways via both cGMP-dependent and independent processes, directly activate calcium-dependent potassium channels, induce protein kinase B (Akt) phosphorylation via the phosphatidylinositol 3-kinase/Akt pathway, and regulate the activity of a variety of hemoproteins by binding to the iron center within their heme prosthetic groups (Kim et al., 2006; Bauer and Pannen, 2009).

Examples of CO-mediated cGMP-dependent activity include inhibition of smooth muscle cell proliferation and platelet aggregation,