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Review

Molecular pathways of mitochondrial dysfunctions: Possible cause of cell death in anesthesia-induced developmental neurotoxicity

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ABSTRACT

The effect of anesthesia on the developing brain has attracted more attention and arguments. This review summarizes various studies on developmental neurotoxicity induced by anesthesia, particularly focuses on the function of the mitochondrial dysfunction. Experimental results present evidence that general anesthesia can cause mitochondrial dysfunction via complex pathways, including oxidative stress, electron transport chain dysfunction, mitochondrial dynamics, calcium homeostasis, and mitochondrion-dependent apoptotic pathway. Hence, the molecular processes of mitochondrial dysfunction should be understood to develop novel therapeutic strategies that can prevent anesthesia-induced neurotoxicity and provide neuroprotection against developmental central nervous system.

Contents

1. Introduction

Millions of pregnant women, newborns, and infants undergo general anesthesia to prepare for surgical or diagnostic procedures each year (Loepke and Soriano, 2008; Anand and Soriano, 2004). Anesthetic agents are administered during an important period of brain growth known as brain growth spurt, this stage occurs from the last three months of pregnancy until approximately two years after birth (in humans) or during the first two weeks after birth (in mice and rats) (Rice and Barone, 2000). Thus, intravenous anesthetics, such as propofol, ketamine and midazolam, or inhalational anesthesia agents including isoflurane, sevoflurane and desflurane, both can induce widespread neuronal death and cause long-term neurocognitive dysfunction regardless if administered in combination or individually (Fredriksson et al., 2004, 2007). Although the underlying mechanisms remain unknown, anesthesia-induced developmental neurotoxicity has been the focus of studies by

Abbreviations: ROS, reactive oxygen species; mtDNA, mitochondrial DNA; ETC, electron transport chain; ER, endoplasmic reticulum; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; VDAC, voltage dependent anion-selective channel; GA, general anesthesia; ATP, adenosine triphoshate; MMP, mitochondrial membrane potential.

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experts specializing in anesthesia-related fields, public individuals and regulatory authorities. In 2011, approximately half of the pediatric papers in *Anesthesiology* are related to the neurotoxicity of general anesthetics in the developing brain (Davidson, 2012).

Mitochondria are cell organelles implicated in the energy production of eukaryotic cells to maintain normal cellular function and amplify cell death signals. Furthermore, these cell organelles mainly generate Adenosine Triphoshate (ATP) required by cells via oxidative phosphorylation; the mitochondria are also involved in other metabolic processes, such as fatty acid metabolism, tricarboxylic acid cycle and heme synthesis. Moreover, the mitochondria are involved in Ca^{2+} and redox homeostatic mechanisms, which are dysregulated during cell death; these cell organelles also release pro-apoptotic proteins, such as cytochrome *c*, apoptosis inducing factor (AIF), after mitochondrial membrane permeabilization and cristae remodeling occur (Rizzuto et al., 2000; Scorrano, 2009). Therefore, mitochondrial dysfunction can result in various diseases affecting cardiovascular and endocrine systems, particularly, neurodegenerative diseases, because neurons are particularly dependent on the mitochondria for their high energy metabolism requirements. As such, studies have shown that mitochondrial dysfunction is involved in the development and progression of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease, these diseases are related to severe cognitive decline (Bennett, 2005; Reddy, 2007; Trushina et al., 2004).

Mitochondrial dysfunction also involves in anesthetic neurotoxicity, for example, propofol markedly decreases oxygen consumption and ATP production in brain synaptosomes (Webb and Elliott, 1951). Inhalational anesthetic agents also elicit similar depressant effects on mitochondrial respiration in vitro (Hall et al., 1973; Einarsdottir and Caughey, 1988). With these findings, a novel understanding of mitochondrial biology has emerged from multiple disciplines; this advancement is very relevant to anesthesia-induced neurotoxicity. Therefore, we summarized the perspectives from different aspects of mitochondrial function to provide relevant information as basis of future studies and elucidate this serious issue.

Anesthesia-induced neurotoxicity associated with mitochondrial dysfunction can be grouped into two categories: (1) mitochondrial disorders directly impairing the vulnerable developmental neural system and (2) aberrant mitochondria affecting the normal function of other organelles, such as endoplasmic reticulum (ER), and indirectly causing cell death in neonatal brain. This review mainly focused on the first category, particularly on mitochondrial oxidative stress, mitochondrial dynamics defects, calcium homeostasis disorder with mitochondrial dysfunction and mitochondrion-dependent apoptotic pathway. This study also aimed to determine the underlying mechanisms of mitochondrial molecular pathways involved in anesthesia-induced developmental neurotoxicity.

2. Effect of mitochondrial oxidative stress in anesthesia-induced developmental neuronal toxicity

The nervous system is susceptible to oxidative stress because of high amounts of polyunsaturated fatty acid, high energy requirements, and relatively low levels of antioxidant pathways (Muravchick and Levy, 2006). The developing brain in the period of instability exhibits a high degree of plasticity. Mitochondrial bioenergetics is also involved in the cellular effects of anesthetics and analgesics (Orestes et al., 2011). Studies have further proposed that anesthetics can induce oxidative stress and mitochondrial dysfunction in the developing brain. For example, treatment with 2% isoflurane for 6 h can increase reactive oxygen species (ROS) accumulation in vitro (Zhang et al., 2010). Furthermore, significant results have been showed that ROS is upregulated and can be significantly decreased by an ROS scavenger EUK-134, in the subiculi of rats exposed to general aneatheisa (midazolam, 9 mg/kg + 0.75% isoflurane + 75% nitrous oxide + 24% oxygen) at post-natal day 7. Moreover, EUK-134 and a mitochondrial protector (PPX) can alter general anesthesia (GA) induced long-term cognitive impairment (Boscolo et al., 2012). Similarly, another ROS scavenger, Trolox, which can significantly attenuate an increase in ketamine induced ROS production in neural stem cells (NSCs) (Bai et al., 2013). In addition, ROS accumulation in mitochondria induced anesthetics is related to exposure duration. One study showed that 2% isoflurane for 60 or 90 min, but not 15 or 30 min, enhanced ROS accumulation in vitro (Sun et al., 2014).

In addition to direct up regulation of ROS production, anesthetics directly damage the neuronal mitochondrial respiratory chain. For example, volatile anesthetics, including halothane, isoflurane and sevoflurane, inhibit mitochondrial complex I activity (Hanley et al., 2002). Other studies have shown that high concentrations (>10 μg/mL) of fentanyl and remifentanil in isolated brain mitochondria can interfere with mitochondrial complexes III and IV, as well as with mitochondrial phosphorylation unit (complex V), such interferences result in a depression of respiratory rates and ATP synthesis (Vilela et al., 2009). In rat and human cerebrocortical synaptosomes, the volatile agent sevoflurane and intravenous anesthetics inhibit complex V activity (Bains et al., 2009a). However, limited reports have presented that anesthetics can inhibit mitochondrial respiratory complex II activity. Mitochondrial complexes I, III, IV, and V are encoded by nuclear DNA and mitochondrial DNA (mtDNA); complex II is the only complex that does not contain any mtDNA-encoded subunits (Falkenberg et al., 2007). This finding can be attributed to the interference of anesthetics with mtDNA mutation; mtDNA mutations also cause neurodegenerative disorders, such as Parkinson's disease (Muller et al., 2013). Thus, this process can be utilized to explore underlying mechanisms.

Why are anesthetics prone to inhibit ETC? Considering that mitochondria are double-lipid membrane-bound organelles and respiratory complexes are immersed in the inner lipid membrane, thus the more severe mitochondrial toxicity induced by anesthetics may be due to a higher lipossolubility, which resulte in an increased effective concentration (Vilela et al., 2009). Defects in ETC occur during critical developmental stages leads to high amounts of ROS production indirectly. These results indicate that early and long duration exposure to anesthetics causes the susceptibility of developing neurons to ROS accumulation inside mitochondria, which then increase in mitochondrial membrane potential (MMP) depolarization, morphological changes and DNA damage by direct contact or through lipid peroxidation, ultimately leading to apoptosis (Zhang et al., 2010; Khatun et al., 2013), which we will discuss in the following paragraphs. Thus, preventing excessive ROS accumulation may be an essential step to protect mitochondria for safe use of GA during early stages of brain development.

3. Mitochondrial dynamics pathway of mitochondrial dysfunction in anesthetic-induced developmental neurotoxicity

3.1. Mitochondrial dynamics defects in the nervous system

In normal mammalian cells, mitochondria are highly dynamic organelles. This dynamic phenomenon is regulated by a delicate balance between two opposing processes: fission and fusion (Chan, 2006; Knott et al., 2008). Mitochondrial fission produces two spherical daughter mitochondria accompanied with cristae and other remodeled inner structures. Although the precise mechanisms are