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Anesthetic neurotoxicity: Apoptosis and autophagic cell death mediated by calcium dysregulation

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Abstract

A number of findings suggested that general anesthetics induced neural cell death by apoptosis in various animal models. Although clinical evidence regarding the correlation between anesthetic exposures at young age and subsequent cognitive impairments remains unclear, repeated or consistent exposures to general anesthetics may be a potential harmful risk in developing human brains. The mechanisms underlying the anesthetic neurotoxicity have received extensive attention recently. We will attempt a brief review to summarize current understanding on the role of both apoptosis and autophagic cell death mediated by calcium dysregulation in anesthetic neurotoxicity.

Keywords

Anesthesia; Anesthetics; Autophagy; Calcium; Apoptosis; Neurodegeneration

The neurotoxic effects of general anesthetics (GAs) have been widely concerned ever since the report of halothane-related morphologic changes and functional deficits of the brain in rats (Uemura et al., 1985) and the striking finding of anesthetics mediated apoptosis in developing brains (Jevtovic-Todorovic et al., 2003). Accumulating evidence suggested that many anesthetics including midazolam (Young et al., 2005), ketamine (Fredriksson et al., 2004; Garcia et al., 2003; Hayashi et al., 2002; Slikker et al., 2007; Young et al., 2005; Zou et al., 2009a; Zou et al., 2009b), propofol (Cattano et al., 2008; Pesic et al., 2009; Vutskits et al., 2005), isoflurane (Istaphanous et al., 2011; Loepke et al., 2009; Ma et al., 2007; Nikizad et al., 2007; Palanisamy et al., 2011; Sanders et al., 2009), sevoflurane (Istaphanous et al., 2011; Satomoto et al., 2009; Zhang et al., 2008), and desflurane (Istaphanous et al., 2011),

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Conflict of interest

The authors report no conflict of interest.

induced neural cell death by apoptosis in various tissue cultures and animal models. In particular, a number of animal studies revealed that excessive anesthesia exposures in the developing brains may impair neurodevelopment and cause long-term neurocognitive deficits (Hayashi et al., 2002; Zou et al., 2009a). Although clinical evidence regarding the correlation between anesthetic exposures at young age and subsequent cognitive impairments remains unclear, multiple or prolonged exposures to anesthetics may be a potential harmful risk in developing human brains (Flick et al., 2011; Sprung et al., 2012). Therefore, the mechanisms underlying the anesthetic neurotoxicity are of great importance to guide the use of general anesthesia safely in patients. In this brief review, we have focused on the summary of current knowledge on different types of cell death (Type 1 apoptosis *vs.* type 2 autophagic cell death) mediated by calcium dysregulation in anesthetic neurotoxicity.

Intracellular Ca^{2+} serves as a biological messenger that is involved in controlling almost all cell processes, including muscle contraction, exocytosis, proliferation, differentiation, protein synthesis, and gene expression, etc (Berridge et al., 2003). Therefore, maintenance of calcium homeostasis plays a crucial role for cell survival. Under physiological conditions, the concentration of cytosolic free calcium ($[Ca^{2+}]_c$) fluctuates at around 100 nM, much lower than that in endoplasmic reticulum (ER) (~300 to 500 μM) and mitochondrion (~0.5 mM), as well as extracellular calcium level (~1.2 mM) (Orrenius et al., 2003). The recent studies indicated that disruption of intracellular calcium homeostasis may be an emerging mechanism involved in anesthetic-induced neuroapoptosis (Joseph, J Donald et al., 2014; Wei, 2011; Zhao et al., 2013). Previous evidence demonstrated that inhalational anesthetics induced cell damage by causing abnormal calcium release from the ER via over-activation of Inositol trisphosphate receptors ($InsP_3Rs$) and/or ryanodine receptors (RyRs) in a concentration- and duration-dependent manner (Inan and Wei, 2010; Joseph, J. D. et al., 2014; Orrenius et al., 2003; Stutzmann et al., 2007; Yang et al., 2008). The increase in the $[Ca^{2+}]_c$ regulates two different self-destructive processes, Type 1 apoptosis and type 2 autophagic cell death (Medina et al., 2015; Orrenius et al., 2003), and whose interaction may determine cell fate (Maiuri et al., 2007) as shown in Fig. 1.

General anesthetics at low concentration for short exposure may activate autophagy to scavenge damaged organelles and remove protein aggregation, as a normal physiological function, and therefore elevating the threshold for apoptosis induction. Zhou *et al.* showed that sevoflurane induced ER stress and activated autophagy, which protected against sevoflurane-induced apoptosis in H4 cells (Zhou et al., 2016). It also been suggested that isoflurane-induced increase in cleaved caspase-3 in the neonatal rat brain can be ameliorated by preconditioning with a brief anesthetic exposure (Peng et al., 2014). Consistent with these findings, it was proposed that adequate promotion of autophagy may play a protective role for cell survival by preventing developmental neurotoxicity of general anesthetics (Li and Yu, 2014). Therefore, the moderate anesthesia that induces protectively autophagic responses may be beneficial for an “adequate” adaptation to potential neurotoxicity of general anesthetics, as referred to adequate anesthesia exposure in Fig.1 (a).

However, contrast to the moderate anesthesia, a prolonged and high concentration exposure of general anesthetics can induce ER stress and subsequent apoptosis and/or excessive autophagy, which eventually results in type I or II cell death respectively. Loepke *et al.*

showed that prolonged isoflurane exposure in neonatal mice led to increased immediate brain cell degeneration (Loepke et al., 2009). It was reported that ER stress pathway mediated isoflurane-induced neuroapoptosis and cognitive impairments in aged rats (Ge et al., 2015). These evidence implicate that aged and developing brain may be more vulnerable to long-term exposure to general anesthetics. It was also suggested that sevoflurane induced apoptosis, degeneration and decreased self-renewal capacity of neural stem cells in a time-dependent way (Nie et al., 2013; Qiu et al., 2015). The overmuch anesthesia that exceed the physiological adaptation of neural cells may be "excessive" and detrimental. As illustrated in Fig 1(b and c), this excessive anesthesia exposure may cause neurotoxicity by inducing apoptosis and/or excessive autophagy.

Excessive autophagy facilitates ATP-dependent events such as phospholipids (PS) exposure and membrane blebbing by producing more ATP, and promoting apoptosis. On the other hand, excessive autophagy may cause cell death directly in a "self-eating" mode (Fig. 1(c)). Apoptosis is a suicidal cell death program, accompanied by caspase activation and degradation of cell component. The caspases trigger the cleavage of multiple proteins including autophagy-related (ATG) proteins to weaken the apoptosis induction and accelerate cell demise (Fig. 1(b)).

As shown in Figure 2, a prolonged exposure of general anesthetics such as isoflurane at high concentration causes Ca^{2+} release from the ER into the cytoplasm by over-activation of $InsP_3Rs$ and/or ryanodine receptor. This may elicit an abnormal rise of $[Ca^{2+}]_c$ and a detrimental decrease of Ca^{2+} level in ER. As protein-folding reaction depends on high concentrations of Ca^{2+} in ER lumen (Görlach et al., 2006), the decreased Ca^{2+} level in ER will result in accumulation of misfolded protein including vATPase, a proton-pumping membrane protein in lysosome. Once vATPase maturation in ER is disturbed, vATPase will fail to drive protons into the lysosome lumen to maintain its proper pH value. That will lead to impaired lysosomal acidification which is essential for macromolecule degradation (Mindell, 2012). Additionally, elevated pH value in lysosome activates transient receptor potential cation channel mucolipin subfamily member 1 (TRPML1), a low H^+-sensitive endolysosomal Ca^{2+} channel, causing Ca^{2+} efflux into cytoplasm (Lee et al., 2015), further aggravating the abnormal elevation of cytosolic Ca^{2+}. In our previous research work, we have demonstrated that isoflurane has greater potency than sevoflurane or desflurane to cause calcium release from the ER and to induce neurotoxicity in different kinds of neurons (Yang et al., 2008). These findings may provide a valuable basis for the clinical use of different inhalational anesthetics in patients, especially for those patients vulnerable to anesthesia-mediated cell damage.

Since mitochondria locate close to ER, the bulk cytosolic free Ca^{2+} released from ER transports into mitochondria via uniporter rapidly, causing mitochondrial Ca^{2+} overload (Gunter and Sheu, 2009; Rizzuto et al., 2009; Szabadkai and Rizzuto, 2004). Abnormally increased Ca^{2+} in mitochondria induces high-conductance permeability transition pores opening in mitochondria (Pinton et al., 2008). Loss of mitochondrial membrane potential, uncoupling of oxidative phosphorylation and release of catabolic hydrolases such as cytochrome c and apoptosis inducing factor (AIF) may occur as a result of increased permeability of mitochondria (Lemasters et al., 2009). The disruption of mitochondrial

respiratory chain will shut down ATP production, resulting impaired ATP-dependent autophagy activity such as autophagosomal lysosome fusion. On the other hand, the components leaked from mitochondria trigger intrinsic apoptotic process. It has been proved that cytochrome c initiates activation of caspase cascade and form apoptosome (McIlwain et al., 2013; Parrish et al., 2013). The impairment of autolysosome function weakens the autophagic cytoprotection and drives process of neuroapoptosis which eventually lead to cell death.

Besides ER calcium release sites, there are several proposed targets for inhaled anesthetics mediated neurotoxicity (Jackson et al., 2016; Wang et al., 2015). Recent studies have proposed the role of p75 growth factor activation on anesthetics mediated neurotoxicity (Pearn et al., 2012). Studies have suggested that general anesthetics may affect the activity of the brain cells via promoting g-aminobutyric acid (GABA) receptors and/or inhibiting N-methyl-D-aspartic acid (NMDA) receptors, since both of them control neurotransmitter transport (de Sousa et al., 2000; Nelson et al., 2002; Sato et al., 2005). Moreover, recent data showed that sevoflurane induced Tau phosphorylation, glycogen synthase kinase 3β activation, and cognitive impairment in the young mice (Tao et al., 2014). It was also suggested that sevoflurane anesthesia in pregnant mice may impair learning and memory in offspring mice by decreasing postsynaptic density-95 levels in the neurons (Zheng et al., 2013). The latest evidence showed isoflurane-induced cognitive deficits may stem from upregulation of hippocampal IL-1b, partially via activation of the canonical NF-κb pathway, in aged rats (Li et al., 2013). Hence, GAs induced neurotoxicity has been appreciated as multifaceted mechanism involving calcium dysregulation, functional alteration of receptors and/or ion channels within plasma membrane, transcription factor dysfunction and some other underlying mechanisms.

In summary, general anesthetics can induce activation of autophagy and apoptosis by disrupting intracellular calcium homeostasis in a time- and concentration- dependent pattern. And the interplay between autophagy and apoptosis may ultimately determine the degree of neural cell injury. Understanding the mechanism of general anesthetics-mediated neurotoxicity will help to develop strategy minimizing the possible harmful effects of GAs in patients, especially in pediatric practice, such as minimizing the total exposure of GAs to patients.

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Highlights

GAs-induced neurotoxicity via disrupting intracellular calcium homeostasis.

Apoptosis *vs.* autophagic cell death are mediated by calcium dysregulation in anesthetic neurotoxicity.

Interplay between autophagy and apoptosis determines degree of neural cell injury.

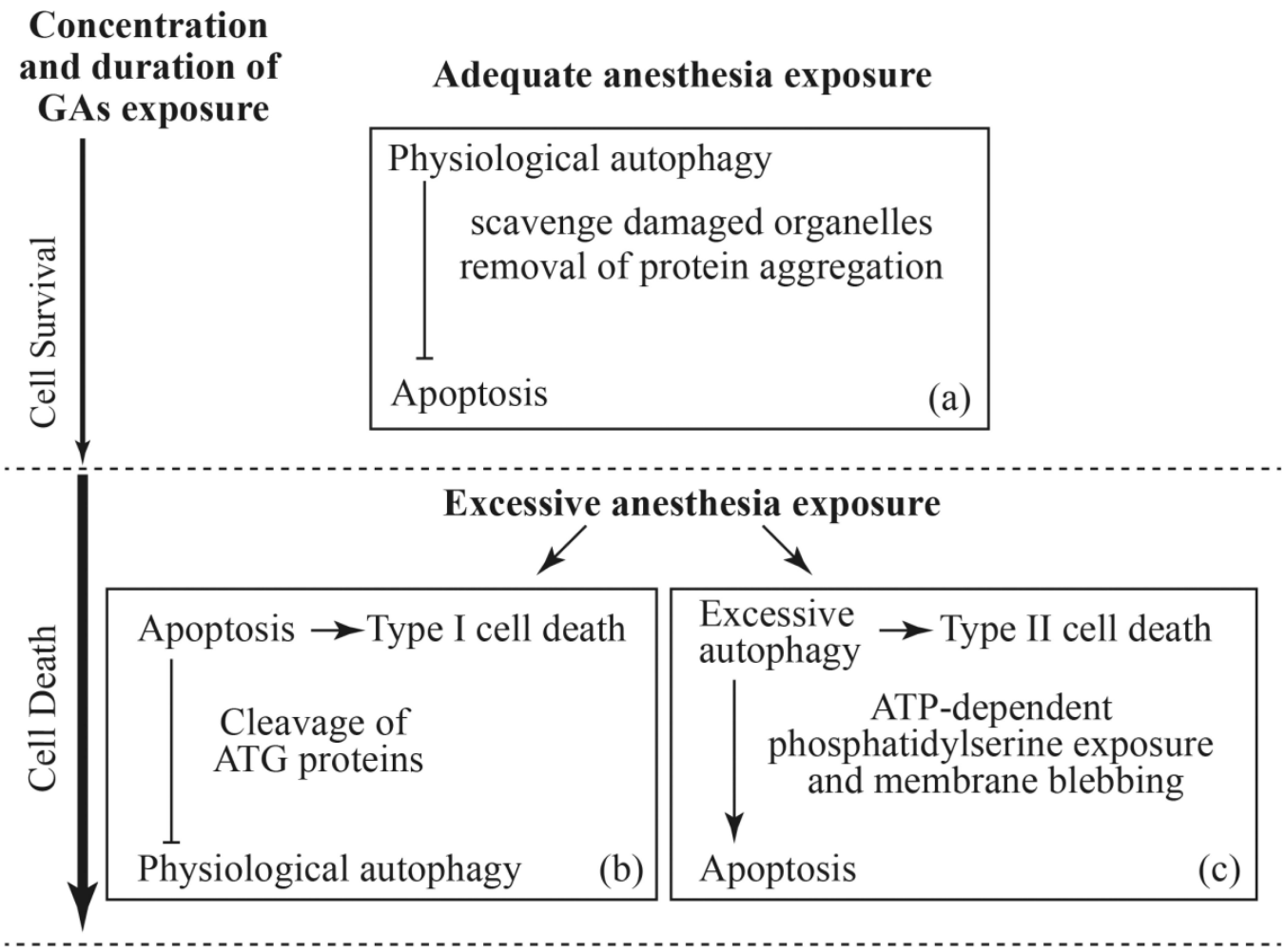

Fig. 1.

Interaction between autophagy and apoptosis induced by general anesthetics with various degrees of concentrations and durations. (a) Physiological autophagy plays a protective role for cell survival by inhibiting apoptosis induction after adequate general anesthetics (GAs) at a low concentration and short exposure. However, excessive GAs at a persistent and high concentration result in type I cell death by apoptosis and inhibit protective autophagy activity via cleavage of ATG protein required for autophagy (b), and over-activated autophagy that cause type II autophagic cell death and aggravation of apoptosis (c).

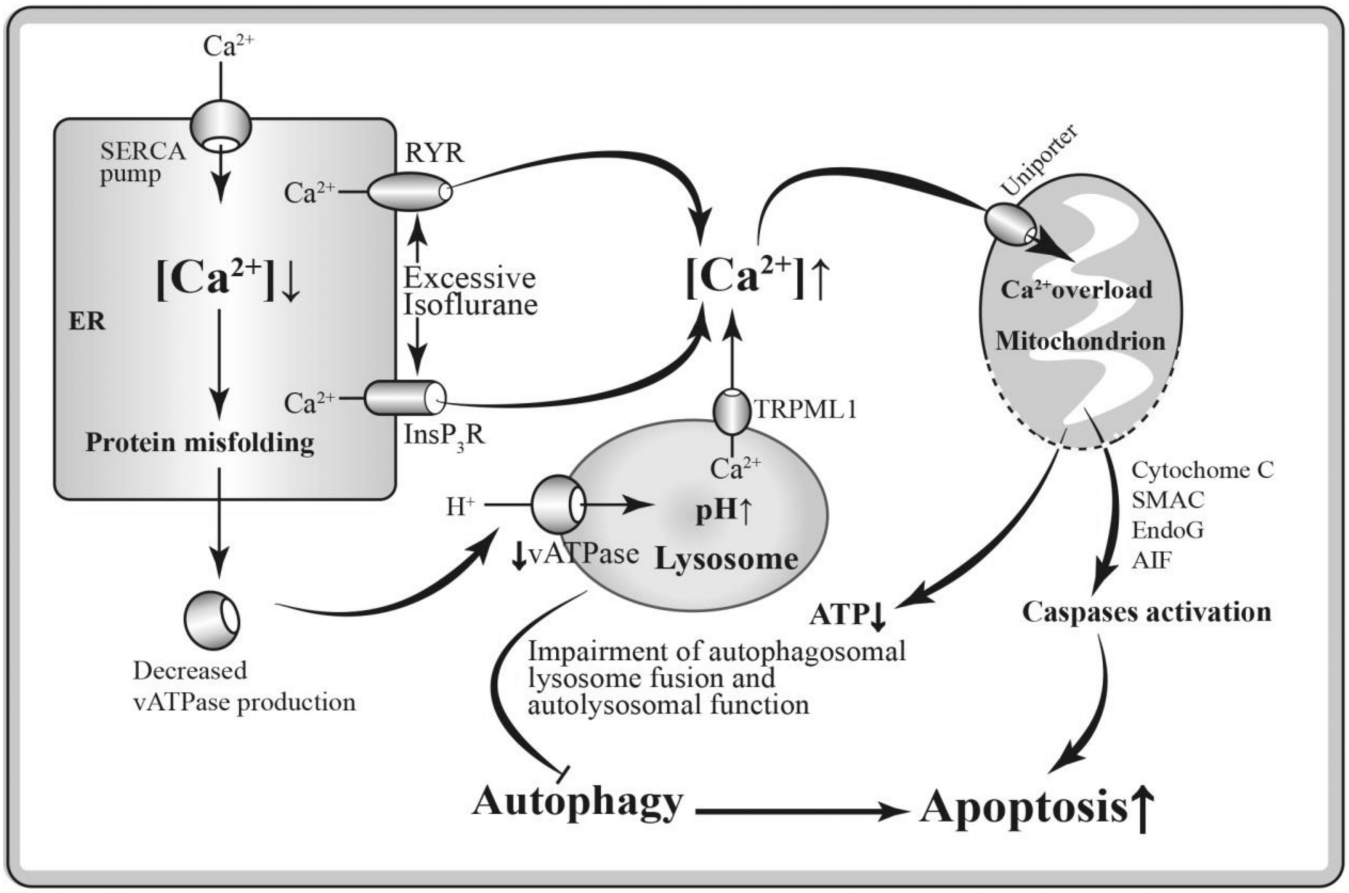

Fig. 2.

Hypothetical pathways of anesthetic neurotoxicity via impaired autophagy secondary to intracellular Ca^{2+} dysregulation. A prolonged exposure of GAs such as isoflurane at high concentration induces excessive Ca^{2+} release from the ER into the cytoplasm by over-activation of $InsP_3Rs$ and/or ryanodine receptor (RYR). The decreased Ca^{2+} level in ER causes accumulation of misfolded protein including vATPase, resulting in elevated lysosomal pH value and impaired autolysosomal function. Abnormally increased cytosolic Ca^{2+} leads to mitochondrial Ca^{2+} overload, and resulting in uncoupling of oxidative phosphorylation and release of catabolic hydrolases such as cytochrome c, apoptosis inducing factor (AIF), endonuclease G (EndoG) and secondary mitochondria-derived activator of caspase (SMAC), and result in apoptosis. In addition, the mitochondrial Ca^{2+} overload may induce decreased ATP production and inhibited ATP-dependent autophagic cytoprotection, thus promoting apoptosis.