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Anesthesia, Calcium Homeostasis and Alzheimer's Disease

Huafeng Wei^{1,*} and Zhongcong Xie²

¹Department of Anesthesiology and Critical Care, University of Pennsylvania, 305 John Morgan Building, 3620 Hamilton Walk, Philadelphia, PA 19104

²Department of Anesthesia and Critical Care, Genetics and Aging Research Unit, Massachusetts General Hospital/Harvard Medical School, 114 16th Street, 3750, Charlestown, MA 02129-4404, USA

Abstract

While anesthetics are indispensable clinical tools generally safe and effective, in some situations there is grown concern about selective neurotoxicity of these agents; the clinical significance is unclear as of yet. The mechanisms for inhalational anesthetics mediated cell damage are still not clear, although a role for calcium dysregulation has been suggested. For example, the inhaled anesthetic isoflurane decreases endoplasmic reticulum (ER) calcium concentration and increases that in the cytosol and mitochondria. Inhibition of ER calcium release, via either IP₃ or ryanodine receptors, significantly inhibited isoflurane neurotoxicity. Neurons made vulnerable to calcium dysregulation by overexpression of mutated presenilin-1 (PS1) or huntingtin (Q-111) proteins showed enhanced apoptosis upon isoflurane exposure. Sevoflurane and desflurane were less potent than isoflurane in altering intracellular calcium, and produced less apoptosis. Short exposures to inhalational anesthetics may provide neuroprotection by preconditioning via a sublethal stress, while prolonged exposures to inhalational anesthetics may induce cell damage by apoptosis through direct cytotoxic effects.

Keywords

Anesthesia; inhalational anesthetics; calcium; Alzheimer's disease; Huntington's disease; neurodegeneration; apoptosis; preconditioning

INTRODUCTION

Each year, more than 200 million people undergo surgery worldwide, most of which are carried out under general anesthesia with an inhaled anesthetic, such as isoflurane, sevoflurane or desflurane. There is growing concern that anesthesia may contribute to delirium and postoperative cognitive dysfunction (POCD) in surgical patients. Accumulating evidence from a variety of cell culture and animal studies suggests that inhaled anesthetics, especially isoflurane, can induce cell damage by apoptosis, although human evidence is still lacking. One potential mechanism underlying anesthetic-induced neural injury could be calcium dysregulation. If true, the developing, aging and/or Alzheimer's brain may be particularly vulnerable to anesthetic-mediated toxicity. The current review will summarize the newly

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* Address correspondence to this author at the Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, 305 John Morgan Building, 3620 Hamilton Walk, Philadelphia, PA 19104, USA; Tel: 215-662-3193; Fax: 215-349-5078; E-mail: weih@uphs.upenn.edu

proposed mechanisms of anesthetic-mediated toxicity by calcium dysregulation, focusing on the Alzheimer's disease model and the previous reviews in this particular area [1-3].

EVIDENCE FOR ANESTHESIA MEDIATED NEURODEGENERATION

Cell and tissue culture

Inhalational anesthetics, especially isoflurane, induce cell damage in various types of tissues and cells, including hippocampal slices [4], lymphocytes [5-8], neuroglioma [9-11], liver cells [12], gingival fibroblasts [13], neurosecretory PC12 cells [14,15], and primary cortical and striatal neurons [5,14,15]. The various *in vitro* models have differing vulnerability to anesthetic toxicity, with lymphocytes generally more vulnerable than neurons [5,14,15]. Also, models made vulnerable to various forms of cell stress, such as cells transfected with genes underlying familial Alzheimer's or Huntington's disease, are unusually sensitive to anesthetic toxicity due to calcium dysregulation [5,15].

Animal studies

Isoflurane, alone or in combination with midazolam or nitrous oxide, was associated with remarkably enhanced apoptosis in the 7-day-old developing rat brain, which was accompanied by subsequent cognitive impairments [16,17]. It is still not clear if anesthetics mediated neurodegeneration contributed to the subsequent impairment of memory and learning in the above animal models. In the elderly rodent, however, isoflurane exposure caused persistent memory impairment [18,19]. Similarly, in the wild type mouse, isoflurane exposure at 12 months of age was associated with subsequent impairment of water maze tasks [20]. Finally, a different inhaled anesthetic, halothane, was associated with increased plaque-load in the Tg2576 transgenic Alzheimer's mouse model [20] only one week after exposure. These studies are important because they demonstrate that during vulnerable periods (the extremes of age); anesthetic exposure alone is capable of causing neuronal injury and/or cognitive dysfunction. The IP₃ receptor antagonist xestospongine C, which inhibits abnormal calcium release from the endoplasmic reticulum (ER), significantly inhibited isoflurane mediated apoptosis in the hippocampus and cerebral cortex of 7-day-old rats (unpublished data). It is not clear at this time what contributes to the vulnerability of different types of neurons to the anesthetic toxicity and if anesthetics induced toxicity with a similar mechanisms in the young developing or aged brains.

Clinical studies

It is difficult to study the neurotoxic effects of anesthetics in patients because of the lack of a robust biomarker for neurodegeneration in the CNS, and the difficulty in obtaining tissue for histological study. Neuropsychological testing is likewise difficult, and the time course of change is not yet clear. However, some clinical data have associated general anesthesia with postoperative cognitive dysfunction (POCD). For example, the incidence of POCD one week after surgery is correlated to the duration of anesthesia [21]. Of greater concern was the observation that persistent POCD is associated with increased mortality [22]. In accordance with animal studies [18,19], age is a significant risk factor for POCD even 3 months after surgery [21]. It is not yet clear whether delirium or POCD represent an unmasking of early Alzheimer's disease (AD) or are predictors of later dementia, but a small retrospective study in Alzheimer patients demonstrated an inverse relationship between surgical experience and the age of onset of AD [23-25]. With respect to other neurodegenerative diseases, case reports suggest that general anesthesia may unmask or accelerate the symptoms of Parkinson's disease [26], while a questionnaire study found that anesthesiologists were more likely to die from Parkinson's disease than age-matched internists [27]. Further animal and clinical studies are necessary to investigate the possibility of anesthetic toxicity, especially in more vulnerable

patients, such as young children, the aged, and those with a genetic predisposition to cognitive disorders [16,17,23,28,29].

ANESTHETICS INDUCE APOPTOSIS BY DISRUPTION OF INTRACELLULAR CALCIUM HOMEOSTASIS

The mechanisms for inhaled anesthetic mediated toxicity in the animal and cell culture studies are still unknown, although the following have been proposed. (1). Inhaled anesthetics increase the production and aggregation of β -amyloid peptide, triggering the neuropathology that underlies the amyloidopathies like Alzheimer's disease [9,30]. Although this mechanism might operate in those at risk of the amyloidogenic neurodegenerative disorders, it seems unlikely to explain anesthetic toxicity in wild type animals, which do not form detectable amyloid [20]. (2). Some studies suggest that activation of GABA receptors in the developing brain may lead to apoptosis and play an important role in the induction of neurotoxicity [16,31,32]. In the immature brain, GABA is the first neurotransmitter to become functional in developing networks and, instead of serving inhibitory neurotransmission as in the adult, GABAergic transmission produces excitation and has a trophic role in neuronal maturation [33]. Therefore, enhancement of GABAergic activity in the immature brain might produce a form of excitotoxicity and apoptotic neurodegeneration [32,33]. Inhalational anesthetics can increase GABA receptor activity [34], and therefore cause excitotoxicity in the immature neurons. (3) NMDA receptor-induced membrane depolarization plays an important role in providing and sustaining neurotrophic support by activation of pro-survival protein kinase signaling pathways [35]. Isoflurane may cause neuronal apoptosis by antagonizing the NMDA receptor [36] and therefore removing the trophic actions of glutamate [16,32]. Although the neurotoxic effects of isoflurane seem to coincide with the period of synaptogenesis [16,35,37], there exists no direct evidence showing that synaptogenesis is itself altered, or is in any way linked to the subsequent cognitive changes. Furthermore, toxic effects of isoflurane, ketamine and nitrous oxide, all possessing NMDA antagonist character, have also been found when exposures occur during adulthood [19,38], a period when synaptogenesis is minimal [29]. Finally, xenon and memantine, two NMDA receptor antagonists, protect against rather than induce neurotoxicity in the developing brain [11,17]. These observations weaken the notion that isoflurane neurotoxicity is due to effects on either GABA or NMDA receptors.

A more recent mechanism proposes that inhalational anesthetics induce apoptosis by a disruption of intracellular calcium homeostasis [5,7,11,15]. The cytosolic calcium concentration ($[Ca^{2+}]_c$) in neurons is tightly maintained at ~ 100 nM, a very low level relative to the extracellular fluid ($[Ca^{2+}]_{EC} \approx 1.2$ mM). The ER is the primary source of releasable intracellular calcium in neurons [39] and plays a very important role in maintenance of intracellular calcium homeostasis, protein synthesis, cell survival and apoptosis [40-43]. As shown in (Fig. 1), excess cytosolic Ca^{2+} is transported into the ER through the action of Ca^{2+} ATPase on the ER membrane, producing ER Ca^{2+} concentrations ($[Ca^{2+}]_e$) of μ M to mM, depending on the cell type [44]. When needed, calcium is released into the cytosolic space through at least two calcium release channels on the ER membrane, the inositol 1,4,5-trisphosphate (IP_3) receptor and the ryanodine receptor [45]. The ryanodine and IP_3 receptors are both calcium release channels. Calcium release from the ER via activation of ryanodine receptors can *affect* IP_3 receptor *activity* and vice versa [46]. It has been proposed that high local concentrations of Ca^{2+} may exist at or close to the ER calcium release sites (e.g. clusters of IP_3 or ryanodine receptors), permitting the mitochondrial uniporter to more efficiently transfer the released calcium into the mitochondria, as opposed to the more diffusely distributed cytosolic calcium entering the cell via other pathways [47]. This regional coupling of ER and mitochondria is more prone to overload the mitochondria with calcium, causing collapse of the mitochondrial membrane potential and induction of apoptosis.

Considerable evidence suggests that inhaled anesthetics can induce calcium release from intracellular calcium stores, although with quite different potency and cell type dependence. For example, isoflurane induces Ca^{2+} release from the sarcoplasmic reticulum (SR) in muscle cells, equivalent to the neuronal ER, probably via activation of the ryanodine receptor [48]. Likewise, in neurons, isoflurane appears to induce calcium release from the ER, but it remains unclear whether this is due to direct or indirect effects on IP_3 or ryanodine receptors [49]. Interestingly, not all anesthetics have the same effect. In the SR, isoflurane generally decreases the Ca^{2+} content [50,51], while sevoflurane has either no effect [52], or actually inhibits Ca^{2+} release [50] and maintains or increases [50] SR Ca^{2+} content [51]. The behavior in neuronal ER seems to be similar. Isoflurane, at equipotent concentrations, induced significantly more of a decline in ER calcium content and a greater elevation of cytosolic and mitochondrial calcium concentrations than either sevoflurane or desflurane. These effects appear to be significantly inhibited by the potent IP_3 receptor antagonist xestospongine C [5,7,15]. In accordance, isoflurane, administered at equipotent concentrations and for equal duration as sevoflurane or desflurane, caused significantly more cell damage by apoptosis secondary to its greater ability to induce calcium release from the ER [7,15].

If inhalational anesthetics directly activate IP_3 (or ryanodine) receptors, the excess calcium may trigger apoptosis, thereby providing a mechanism for anesthetic-induced cytotoxicity. To test the importance of IP_3 receptors in isoflurane-induced apoptosis, it is possible to alter IP_3 activity either genetically or with pharmacologic agents. For example, cultured chicken T lymphocytes with triple knock out of IP_3 receptors were resistant to inhaled anesthetic-induced apoptosis, as well as the decrease in ER calcium concentration and increase in the cytosolic and mitochondrial calcium concentrations [5,7]. In contrast, cells with an elevated IP_3 receptor activity, such as rat pheochromocytoma neurosecretory (PC12) cells transfected with presenilin-1 (L286V) or Q-111 rat striatal neurons (a cell model of Huntington disease) were vulnerable to isoflurane-mediated apoptosis and calcium release from the ER [5,15]. These effects were significantly inhibited by the IP_3 R antagonist xestospongine C [5,15]. Suppression of the IP_3 receptor using siRNA significantly reduced isoflurane-mediated activation of caspase-3 [11]. Finally, in an animal study, the intraventricular injection of xestospongine C significantly inhibited isoflurane-induced apoptosis in the hippocampal CA1 region and cortex in the developing rat brain (*unpublished data*). All these studies suggest that isoflurane-induced activation of the IP_3 receptor may play an important role in anesthetic toxicity.

On the other hand, it is well-known that inhaled anesthetics enhance calcium release from the other major ER calcium release channel, the ryanodine receptor, especially when it contains specific mutations [14,53]. Evidence in favor of its contribution to isoflurane toxicity was the demonstration that a specific antagonist, dantrolene, significantly inhibited isoflurane mediated apoptosis [14] in cell culture models. However, since both the IP_3 and ryanodine receptors interact, it is not yet clear whether one or both are direct targets of isoflurane.

A recent study suggested that calcium influx from the extracellular space also plays a role in isoflurane cytotoxicity [11]. Memantine, a noncompetitive partial antagonist of the NMDA receptor, which inhibits calcium influx via the NMDA receptor, significantly inhibited isoflurane-induced caspase-3 activation, apoptosis and cell death. Isoflurane cytotoxicity can also be ameliorated by lowering the extracellular calcium level by using both extracellular and intracellular calcium chelators (EDTA and BAPTA/AM respectively) to suppress the isoflurane-mediated elevation of cytosolic calcium. Further studies are needed to investigate and understand how the calcium release from ER and/or calcium influx from extracellular space contribute to anesthetic toxicity.

ANESTHETICS WORSEN NEURODEGENERATION IN *MODELS OF ALZHEIMER'S DISEASE*

Since the initial demonstration that inhalational anesthetics can increase aggregation of amyloid β -protein and potentiate β -amyloid mediated cytotoxicity [30], there have been an increasing number of studies investigating how inhalational anesthetics, especially isoflurane, might cause cell death in different models of Alzheimer's disease [5,9,10,15]. In cell culture models, isoflurane can alter the APP processing and increase production of β -amyloid [9,10], which is still thought to be a key feature in the pathogenesis of Alzheimer's disease. Inhalational anesthetics not only increased the aggregation of β -amyloid in tissue culture [25], but also increased senile plaque formation in a transgenic mouse study [20], one of hallmarks of pathogenesis in Alzheimer's disease. As shown in (Fig. 2), it has been proposed that isoflurane activates caspase-3, perhaps via calcium release, thereby inducing apoptosis, which in turn increases the activity of the beta-site amyloid beta precursor protein (APP)-cleaving enzyme (BACE) and the γ -secretase, both of which are responsible for generating the amyloid- β proteins. The isoflurane-mediated elevation and aggregation of amyloid- β proteins then induce further caspase-3 activation and apoptosis to initiate a vicious cycle.

One of the proposed mechanisms of neurodegeneration in Alzheimer's disease is that mutated presenilin-1 (PS1), which is found in more than 50% of the cases of early-onset of familial Alzheimer's disease, increases the activity of the IP3 receptors [54,55] and the number of ryanodine receptors [56], both of which will increase calcium release from the ER upon activation by their agonists. A recent study demonstrated that mutated PS1 and PS2 interact with IP3 receptors and exert profound stimulatory effects on its gating activity in response to IP3, which result in the decreased ER calcium level [57], although there is still controversy on how presenilin mutation affect ER calcium level [57,58]. Presenilin mutation may also affect intracellular calcium regulation by its effects on SERCA pump activity and amyloid beta production [59,60]. Theoretically, neurons containing mutated PS1 will be vulnerable to any agonist that can activate IP3 or ryanodine receptors. This seems to be true as PC12 cells expressing mutated PS1 were vulnerable to isoflurane-induced cell damage and were associated with elevated calcium release from the ER and decrease of ER calcium level, both of which were significantly inhibited by the IP3 receptor antagonist xestospongin C or triple knock out of IP3 receptors [7,15]. Similarly, in a cell model of Huntington's disease, which is thought to include elevated activity of the IP3 receptors [61-63], isoflurane also significantly induced more cell damage and greater calcium release from the ER than in the wild type control cells, which were inhibited by the IP₃ receptor antagonist xestospongin C [5]. These studies suggest that neurons containing specific features of Alzheimer's or Huntington's disease are more vulnerable to calcium dysregulation and subsequent cell damage induced by inhalational anesthetics.

ANESTHETICS MAY BE BOTH NEUROPROTECTIVE AND NEUROTOXIC

Inhalational anesthetics may be both neuroprotective and neurotoxic, depending on the duration and concentrations used. Mild and short periods of calcium release from the ER and moderate elevation of cytosolic calcium concentration caused by exposure to inhalational anesthetics at short durations may trigger the ER stress response, marked by the expression of genes characterizing the well-known "preconditioning" effect [64-66]. However, longer exposures to isoflurane, producing excessive and prolonged calcium release from ER, may deplete ER calcium and shut down protein synthesis leading to "cytotoxicity" effects [5,14,15,41,67]. Inhalational anesthetics, especially isoflurane, have long been considered neuroprotective in various cell culture and animal models [68-72]. Increasing evidence suggests inhalational anesthetics also induce neuronal apoptosis dose- and time-dependently in various cell cultures and in different animal models [4,5,9,14-17,30,73]. A recent study

suggested that, like ischemia preconditioning, short exposure to isoflurane *preconditioned neurons and* protects against neurotoxicity induced by prolonged exposure to isoflurane [65]. In addition, a previous study also demonstrated that Isoflurane's preconditioning ability was dose-dependent and was more obvious in PC12 cells with overexpression of mutated Alzheimer's PS1 [65]. Halothane preconditioning also inhibited isoflurane-induced toxicity, suggesting preconditioning with different inhalational anesthetics may all inhibit isoflurane-induced cell damage. In addition, the potency for preconditioning among inhaled anesthetics may be different. For example, prolonged use of sevoflurane was less toxic than both isoflurane and halothane [6,14,74], but short use of sevoflurane was also less effective for preconditioning and neuroprotection than either isoflurane or halothane [65]. It is important and urgent to study the point at which inhalational anesthetic-mediated cytoprotection becomes cytotoxicity, so that we can best utilize the protective effects and prevent any toxic consequences.

CONCLUSION

It is now clear that inhalational anesthetics, especially isoflurane, induce apoptosis by the disruption of intracellular calcium homeostasis in cell culture systems and perhaps in animals as well. It is also clear that calcium homeostasis plays a central role in neurodegenerative disorders like Alzheimer disease. Thus, these data suggest that a detrimental interaction between anesthetic exposure and Alzheimer's neuropathology may exist, and that drugs specific to calcium signaling may be useful therapeutic approaches.

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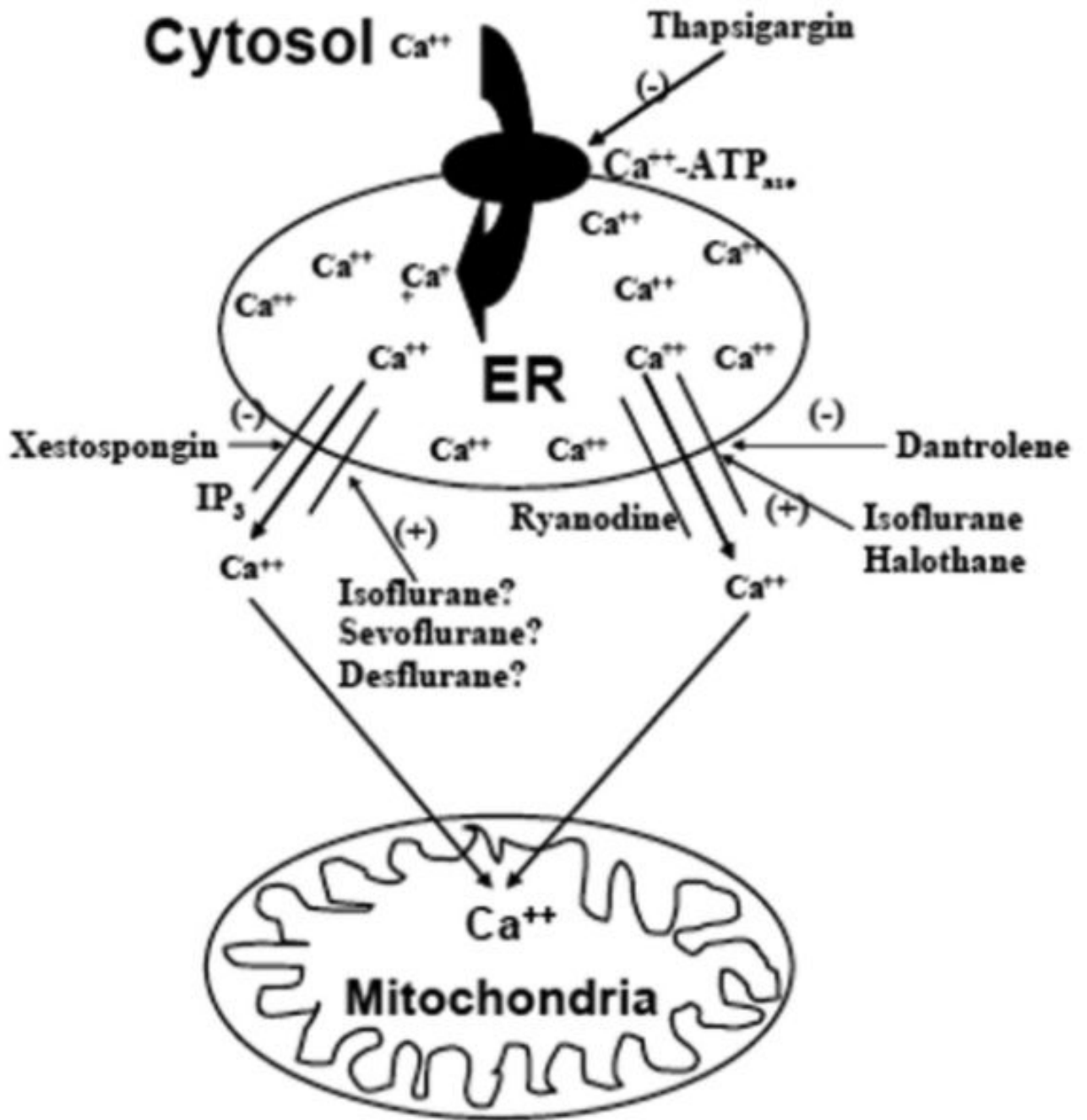


Fig. (1). Dynamics of intracellular Ca^{2+} homeostasis and inhaled anesthetics
 Ca^{2+} released from the endoplasmic reticulum (ER) via IP_3 and/or ryanodine receptors into cytosolic space is constantly pumped back to the ER by Ca^{2+} ATPase on the ER membrane. Dantrolene and xestospongin are antagonists to the ryanodine and IP_3 receptors respectively. Thapsigargin is a selective inhibitor of Ca^{2+} ATPase. Ca^{2+} released from the ER can be transferred to mitochondria as the two compartments are in close proximity.

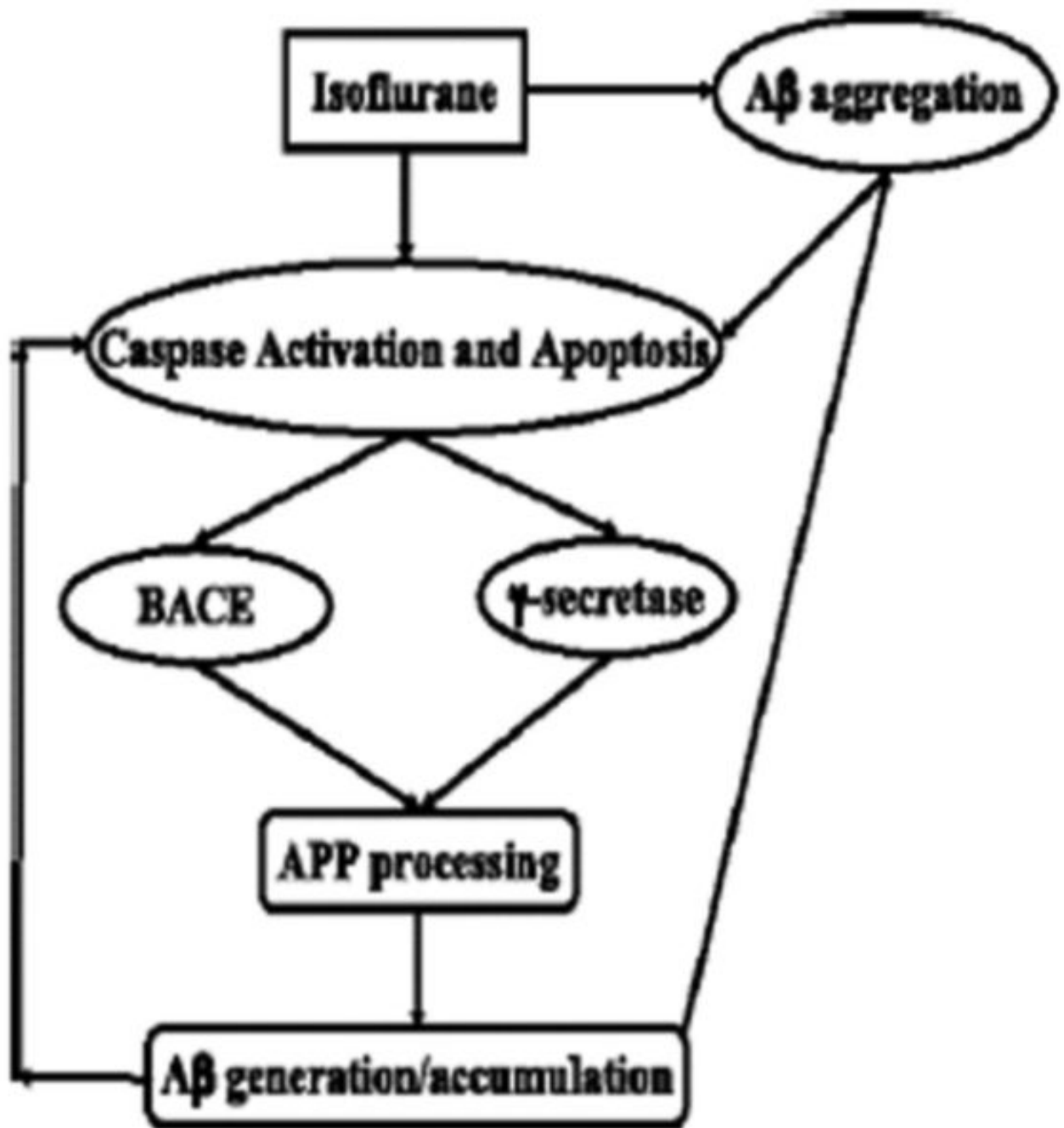


Fig. (2). Hypothetical pathway by which isoflurane induces apoptosis and A β generation and aggregation

Isoflurane induces caspase-3 activation/apoptosis. Caspase activation, in turn, increases the activities of both BACE and γ -secretase, which serve to increase A β generation/accumulation. Isoflurane also enhances A β aggregation, which induces further caspase-3 activation and apoptosis. Elevated A β generation/accumulation and A β aggregation then further induce apoptosis. Cited with permission from Xie *et al.*, *J. Neurosci*, 2007; 27:1247-54.