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Inhalational Anesthetics as Preconditioning Agents in Ischemic Brain

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SUMMARY

While many pharmacological agents have been shown to protect the brain from cerebral ischemia in animal models, none have translated successfully to human patients. One potential clinical neuroprotective strategy in humans may involve increasing the brain's tolerance to ischemia by pre-ischemic conditioning (preconditioning). There are many methods to induce tolerance via preconditioning such as: ischemia itself, pharmacological, hypoxia, endotoxin, and others. Inhalational anesthetic agents have also been shown to result in brain preconditioning. Mechanisms responsible for brain preconditioning are many, complex, and unclear and may involve Akt activation, ATP-sensitive potassium channels, and nitric oxide, amongst many others. Anesthetics, however, may play an important and unique role as preconditioning agents, particularly during the perioperative period.

INTRODUCTION

Previous exposure of the brain to minor insults, chemicals, or pharmacological agents can “precondition” or increase the brain's tolerance to future, more injurious events. This acquired tolerance can be induced transiently and rapidly or in a delayed and sustained fashion, suggesting that multiple mechanisms may be involved. Virtually any stimulus used to induce brain injury or alter brain function can be applied in a milder form to potentially precondition the brain (Table 1). Inhalational anesthetic preconditioning is considered to be a type of chemical preconditioning in brain [1].

Anesthetic preconditioning of the brain during neurosurgical and cardiovascular surgeries may prevent or delay neurological complications like perioperative stroke. Perioperative stroke is a serious complication that can occur during or following procedures such as carotid endarterectomy (CEA), which has a reported perioperative stroke incidence from 0.25% to 7% [2,3]. According to the North American Symptomatic Carotid Endarterectomy Trial, 35% and 65% of perioperative strokes occurred during or after CEA, respectively [4]. Approximately 56% of these post-procedural strokes occurred within 24 hours after CEA [4]. Studies evaluating volatile anesthetics may identify new and more medically feasible means of conditioning a brain that might be exposed to ischemic or mechanical injury from surgery and other interventional procedures.

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This review will discuss the most recent research concerning inhalational anesthetic effects before (preconditioning) rather than during (neuroprotection) ischemic brain injury. Currently utilized models of volatile anesthetic preconditioning in ischemic brain will be described in terms of the types of inhalational anesthetics, ischemic models, and animal species used as well as length and frequency of preconditioning, intervals between preconditioning and cerebral ischemia, and outcomes. The preconditioning actions of isoflurane, sevoflurane, halothane, and xenon (Table 2) will be evaluated along with potential mechanisms underlying volatile anesthetic preconditioning effects. The role of gender and age on brain preconditioning with inhalational anesthetics will also be examined. Lastly, future research directions for volatile anesthetics as preconditioning agents in ischemic brain will be discussed.

ANIMAL MODELS

The following issues should be considered when developing or utilizing animal models to evaluate inhalational anesthetic preconditioning effects and mechanisms in ischemic brain: anesthetic agent and dose; ischemic model; animal species; preconditioning length and frequency; interval between preconditioning and cerebral ischemia; and outcomes (Table 3). Current research has focused mostly on isoflurane (1% to 2.25%) [5–13] primarily due to availability, cost, and clinical relevance but also includes sevoflurane (2% to 4%) [14,15], halothane (1% to 2%) [5,16] and xenon (70%) [17] (Table 3). Several focal (1 to 2 hours transient middle cerebral artery occlusion, MCAO [6–8,10,16]; 6 h to 4 days permanent MCAO [5,9]) and global (7 to 8 minutes cardiac arrest [11,14]; 10 minutes bilateral carotid artery occlusion + hypotension [15]; 1 to 2.5 hours hypoxia-ischemia [12,13,17]) stroke models have been used primarily in rodents (rats, mice) [5–10,12–17], with very few studies in nonrodent species (dog) [11]. Preconditioning period length has ranged from 30 minutes to 4 hours while the frequency has varied from a single exposure to daily exposure up to 5 consecutive days (Table 3). The protective effects of inhalational anesthetic preconditioning have been observed when preconditioning occurs from 0 to 24 hours before cerebral ischemia (Table 3). Histopathology and neurological function are the most commonly used endpoints for assessing the preconditioning effects of inhalational anesthetics in ischemic brain (Table 3). Outcomes have been measured from approximately 1 day to 3 months post-ischemia in preconditioned brains [5–17].

INHALATIONAL ANESTHETIC PRECONDITIONING EFFECTS

Isoflurane

Isoflurane has been the most extensively studied inhalational anesthetic brain conditioning agent. Isoflurane preconditioning before permanent or transient focal cerebral ischemia reduced brain injury in male rodents [5–9] but either worsened or had no effect on infarct volume in female mice [10]. In global ischemia, isoflurane pretreatment improved neurological deficit scores in female dogs [11]. Isoflurane preconditioning before hypoxia/ischemia also decreased preweaning mortality, attenuated neonatal rat brain cell loss and damage, and improved adult striatal function [12,13]. These studies suggest that isoflurane preconditioning can be neuroprotective, neutral, or detrimental depending on the experimental ischemic model.

Sevoflurane

Current research on sevoflurane preconditioning has been limited to global ischemic brain injury. In global cerebral ischemia, sevoflurane pretreatment diminished neuronal damage in male rats [14,15]. It is unknown if sevoflurane preconditioning could have neuroprotective effects in other types of brain ischemia.

Halothane

Preconditioning with halothane before permanent or transient focal stroke reduced infarction volume in male rats [5,16]. However, the decreased availability of halothane and the accessibility of alternative volatile anesthetics with fewer systemic side effects make it unlikely that additional research evaluating halothane preconditioning will be pursued.

Xenon

Xenon, a chemical element (atomic number 54) and a noble gas, has only recently been investigated as a brain preconditioning agent. Xenon-induced preconditioning before hypoxia-ischemia in neonatal rats decreased infarction size and improved neurological function [17]. Xenon's use clinically as an anesthetic or as a preconditioning agent is currently restricted by its high cost, limited availability, and lack of a delivery system with gas recycling capabilities.

Summary

Brain preconditioning with isoflurane, sevoflurane, halothane, and xenon has generally yielded neuroprotective effects in ischemic brain (Table 3).

PRECONDITIONING MECHANISMS

Anesthetic preconditioning mechanisms are likely to be complex and interdigitated. Molecular and cellular mechanisms of volatile anesthetic action may partly explain the preconditioning effects of these agents. However, there may be unique or common mechanisms underlying anesthetic preconditioning compared with other types of brain preconditioning. Table 4 lists candidate mechanisms based on research concerning volatile anesthetic and other types of preconditioning in ischemic brain and heart [1,18–22]. For the purposes of this review, only selected mechanisms with supporting *in vivo* and *in vitro* evidence will be discussed. Many of the other potential anesthetic preconditioning mechanisms have yet to be validated *in vivo* or remain speculative.

ATP-Sensitive Potassium (K_{ATP}) Channels

Evidence from ischemic preconditioning models in heart indicates that opening of K_{ATP} channels alters reactive oxygen species (ROS) production, diminishes intra-ischemic mitochondrial calcium accumulation, and enhances post-ischemic mitochondrial energy production [23]. Furthermore, one study examining isoflurane preconditioning mechanisms in ischemic rabbit myocardium suggests that opening of K_{ATP} channels acts as a preconditioning trigger through ROS generation [24]. These proposed protective mechanisms for ischemic and anesthetic preconditioning in myocardial ischemia may apply to inhalational anesthetic preconditioning in ischemic brain since several studies utilizing K_{ATP} channel blockers have shown attenuation of beneficial isoflurane and sevoflurane preconditioning effects in cerebral, cortical, and hippocampal ischemic and hypoxic models [8,25–27]. Interestingly, blocking K_{ATP} channels had no effect on isoflurane preconditioning neuroprotection in ischemic cerebellar slices [28], suggesting that there may be regional variations in brain K_{ATP} channel distribution and activation.

Nitric Oxide (NO)

Depending on the amount and production origin, NO can have favorable or damaging effects in ischemic brain [29]. Endothelial and inducible nitric oxide synthase (iNOS) have been implicated in protection induced by ischemic preconditioning in brain [30,31]. Two studies evaluating ischemic neuronal injury in rat imply that isoflurane preconditioning neuroprotection is iNOS-dependent [5,12]. Unfortunately, little is known about the role of endothelial and neuronal NOS in an ischemic brain preconditioned with volatile anesthetics as

well as the progression of NOS isoform induction and NO production for different inhalational anesthetics over time.

Akt Activation

Akt is a serine-threonine kinase whose activation via phosphorylation can control the balance between survival and death signaling in brain [32]. Several laboratories have shown that non-anesthetic, neuroprotective forms of brain preconditioning enhance Akt activation after cerebral ischemia in male and neonatal animals [31,33–36]. Only one study in a male mouse model of isoflurane preconditioning has shown that anesthetic preconditioning can induce brain Akt activation before ischemic injury occurs, potentially altering ischemic sensitivity, and that the neuroprotection from anesthetic preconditioning in ischemic brain is Akt isoform (Akt1)-dependent [10].

GENDER AND AGE EFFECTS ON PRECONDITIONING

Women may have a greater perioperative stroke risk than men [37–39]. A recent review of randomized and non-randomized trials evaluating gender and age and stroke risk following CEA concluded that operative stroke risk is increased in women independent of age [40]. While gender and age are known to alter experimental ischemic brain outcomes [41,42], few studies have examined gender and age in preconditioned brain exposed to ischemic and other types of brain injury.

Investigational studies examining anesthetic and other forms of preconditioning in ischemic brain have used primarily young male animals. However, several studies suggest that the brain preconditioning response differs between genders and age groups. For example, a study in isoflurane preconditioned mice subjected to transient focal stroke showed exacerbation of or no protection from ischemic injury in young and middle-aged females, respectively, but reduced ischemic injury in comparably aged males [10]. Studies on hypoxic tolerance of mouse hippocampal slices chemically preconditioned with 3-nitro-propionate suggest that hypoxic tolerance and preconditioning are gender-dependent and modulated by gender-specific mechanisms [43,44]. Unfortunately, two studies which evaluated anesthetic and ischemic preconditioning in young female dogs [11] and aged gerbils [45], respectively, did not utilize age-matched males for comparison of gender and age preconditioning effects in ischemic brain. Likewise, in several neonatal hypoxia-ischemia studies, less brain damage and improved function was seen in isoflurane and xenon preconditioned rats but these findings were not stratified by gender [12,13,17].

These results suggest that gender and age may modify an injured brain's response to inhalational anesthetic preconditioning. However, the underlying mechanisms for gender and age differences in volatile anesthetic effects on perioperative stroke risk are unknown and offer potential factors for optimizing anesthetic management of patients undergoing procedures at risk for perioperative stroke.

CONCLUSIONS

Whether inhalational anesthetics offer perioperative ischemic brain protection and which agents are the best preconditioning agents remain open questions. Future research should focus on dose, timing, and duration of anesthetic preconditioning as well as the severity of ischemic brain injury on preconditioned brain outcomes. Studies concerning long-term consequences and volatile anesthetic preconditioning mechanisms in ischemic brain also need to be performed if we are to translate findings to human patients and improve the direction and design of future clinical trials. In addition to examining inhalational anesthetic- and species-specific effects, investigators should evaluate age- and gender-specific responses and mechanisms for

experimental volatile anesthetic preconditioning outcomes. The role of inhalational anesthetics in the morbidity and mortality of human perioperative stroke is unclear because of limited clinical information on inhalational anesthetics, perioperative stroke risk and neurological outcomes for surgical procedures. More prospective, randomized clinical trials are needed that compare the long-term consequences of different volatile anesthetic agents on perioperative stroke and outcomes for at risk surgical procedures.

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Table 1**Brain Preconditioning Stimuli**

Stimulus	References
Analgesics	[46]
Anesthesia	[1,19]
Chemical/Pharmacological	[47]
Endotoxins	[48]
Hyperoxia	[49]
Hypoxia	[43,44,50]
Hyperthermia	[51]
Hypothermia	[52]
Ischemia	[20,21,42,45]
Seizures	[53]

Table 2

Formulae and structures of inhalational anesthetics used as preconditioning agents in ischemic brain

Agent	Formula	Chemical Structure
Isoflurane	$\text{CF}_3\text{CHClOCHF}_2\text{H}$	$ \begin{array}{ccccc} & \text{F} & \text{H} & & \text{F} \\ & & & & \\ \text{F} & - \text{C} & - \text{C} & - \text{O} & - \text{C} - \text{H} \\ & & & & \\ & \text{F} & \text{Cl} & & \text{F} \end{array} $
Halothane	$\text{H}_2\text{FCOCH}(\text{CF}_3)_2$	$ \begin{array}{ccccc} & \text{H} & \text{H} & & \\ & & & & \\ \text{H} & - \text{C} & - \text{O} & - \text{C} & - \text{CF}_3 \\ & & & & \\ & \text{F} & \text{CF}_3 & & \end{array} $
Sevoflurane	CHClBrCF_3	$ \begin{array}{ccccc} & \text{F} & \text{Cl} & & \\ & & & & \\ \text{F} & - \text{C} & - \text{C} & - \text{H} \\ & & & & \\ & \text{F} & \text{Br} & & \end{array} $
Xenon	Xe	$ \begin{array}{c} \text{Xe}_{54\text{P}} \\ 77\text{N} \end{array} $

Table 3

Animal Models of Inhalational Anesthetic Preconditioning in Ischemic Brain

Inhalational Anesthetic	Anesthetic Dose	Ischemic Model	Animal Species	Preconditioning Length and Frequency	Interval Between Preconditioning and Ischemia	Preconditioning Effects and Outcomes	References
Isoflurane	1.4% 1.5%, 2%, 2.25%	Permanent focal ischemia	Male Wistar rats	3 h	0, 12, or 24 h	↓ infarction volume	[5]
		Transient focal ischemia	Male Sprague-Dawley rats	1 h daily for 5 days	24 h	↓ infarction volume	[8]
	1.5%	Hypoxia-ischemia	7 day old Sprague-Dawley rats	30 min	24 h	↓ brain loss and damage	[12]
	2%	Permanent focal ischemia	Male Sprague-Dawley rats	30 min	24 h	↓ brain infarct size; improved neurological deficit scores	[9]
	1.5%	Transient focal ischemia	Male Sprague-Dawley rats	1 h	1 h	↓ brain infarct volumes; improved neurological deficit scores	[7]
	1%	Transient focal ischemia	Male C57BL/6 mice	3 h	0, 12, or 24 h	↓ infarct volume	[6]
Sevoflurane	1%	Transient focal ischemia	Young and middle aged male and female C57BL/6 mice	4 h	24 h	↓ infarction volume in males; ↑ infarction volume in young females; no effect in middle-aged females	[10]
	1.8%	Hypoxia-ischemia	9-day-old C57x129T2 F1 mice	2 h	24 h	↓ preweaning mortality; improved adult striatal neurochemical scores	[13]
	1.5%	Global ischemia	Female beagle-like dogs	30 min	0 h	Improved neurological deficit scores	[11]
	2.4%	Global ischemia	Male Sprague-Dawley rats	30 min daily for 1 or 4 days	15 min (single preconditioning exposure) or 24 h (4 preconditioning exposures)	↓ ischemic neuronal damage	[14]
Halothane	2%, 4%	Global ischemia	Male Wistar rats	1 h	30 min	↓ ischemic neuronal damage	[15]
	1.2% 1% to 2%	Permanent focal ischemia	Male Wistar rats	3 h	24 h	↓ infarction volume	[5]
		Transient focal ischemia	Male Wistar rats	1 h	0 h	↓ infarction volume	[16]
Xenon	70%	Hypoxia-ischemia	7-day-old Sprague-Dawley rats	2 h	4, 8 or 24 h	↓ infarct size; improved neurological function	[17]

Table 4
Candidate Inhalational Anesthetic Preconditioning Mechanisms

Proposed Mechanism	References
Akt activation	[1,10,20,22,33–36]
ATP-sensitive potassium channels	[1,8,19,21–27]
Nitric oxide and inducible nitric oxide synthase	[1,5,12,19,20,31]
Inhibition of glutamate release	[1,19–21]
Calcium-dependent processes	[1,11]
Anti-apoptotic mechanisms	[1,17,19,22]
Reactive oxygen species	[1,22]
Cerebral blood flow	[1]
Extracellular signal-regulated kinase (ERK)/Early growth response gene 1 (Egr-1)/Bcl-2 pathway	[18,22]
Adenosine A ₁ receptor activation	[1,7,19–21]
p38 mitogen-activated protein kinases	[1,9]