Brain protection by anesthetic agents

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Purpose of review

Patients at risk for perioperative stroke, or those who have suffered recent cerebral injury, may benefit from neuroprotective properties of anesthetic agents during surgery. This manuscript reviews recent clinical and experimental evidence for neuroprotective effects of common anesthetic agents, and presents potential mechanisms involved in anesthetic neuroprotection.

Recent findings

Although strong experimental data support a neuroprotective potential of several anesthetic agents, specifically isoflurane and xenon, consistent long-term protection by either agent has not been demonstrated. Unfortunately, there is a lack of clinical studies that would support the use of any one anesthetic agent over the others. Mechanisms of neuroprotection by anesthetic agents appear to involve suppression of excitatory neurotransmission, and potentiation of inhibitory activity, which may contribute to the reduction of excitotoxic injury. Activation of intracellular signaling cascades that lead to altered expression of protective genes may also be involved.

Summary

Solid experimental evidence supports neuroprotection by anesthetic agents. It is too early to recommend any specific agent for clinical use as a neuroprotectant, however. Further study is warranted to unravel relevant mechanisms and to appreciate the potential clinical relevance of experimental findings.

Keywords

anesthesia, neuroprotection, neurotoxicity, perioperative cerebral ischemia, posttreatment, preconditioning

Curr Opin Anaesthesiol 19:481–486. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Anaesthesiology 2006, 19:481–486

Abbreviations

NMDA	*N*-methyl-D-aspartate
OGD	oxygen–glucose deprivation

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Introduction

Anesthesiologists routinely care for patients at risk for intraoperative or perioperative cerebrovascular accidents and cerebral ischemia, due to a combination of preexisting cerebrovascular disease or high-risk surgery, such as clipping of cerebral aneurysms, or open heart surgery on cardio-pulmonary bypass. It is obvious that the anesthesia provider will be greatly interested in any effects that his or her choice of anesthetic agents may have on the functional deficit caused in these patients by ischemic events that take place during anesthesia, or shortly thereafter. In addition, a positive or detrimental influence of anesthetic agents on the still evolving brain damage in patients who have recently suffered cerebral injury, and now require surgery, would clearly affect the anesthesia care provided to these patients. Unfortunately, despite a long history of experimental studies and some highly interesting data from recent experimental research, so far, no anesthetic agent that would render profound neuroprotection in humans has been identified in clinical trials.

Change of paradigm in anesthetic neuroprotection

Neuroprotection by anesthetic agents was first described more than three decades ago, when barbiturates were found to reduce neuronal energy consumption by reducing electrical activity. Accordingly, intraoperative neuroprotection by anesthetic agents for many years relied mainly on the reduction of the cerebral metabolic rate of oxygen ($CMRO_2$) by suppressing electric activity, as monitored by electroencephalography.

In parallel to our growing understanding of the many facets of and pathways involved in ischemic cell death, evidence has evolved in recent years that anesthetic agents actually act more specifically, and can interfere with detrimental ischemic cascades beyond a simple reduction of metabolic activity. Various potential mechanisms have been described, including inhibition of excitatory activity and potentiation of inhibitory circuits. Most anesthetics have been found to be antagonists of glutamate at *N*-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptors, and to also potentiate inhibitory γ-amino-butyric-acid (GABA)-A receptor activity [1,2]. In addition, they reduce glutamate release [3,4] and increase glutamate reuptake from the synaptic cleft, thereby attenuating excitotoxic death of neurons. Volatile anesthetics as well as xenon can also open K^+ channels, including the newly described two-pore TREK channel, which causes

neuronal hyperpolarization and contributes to anesthesia as well as to resistance against ischemia [5]. Other important mechanisms potentially involved in neuroprotection by anesthetics include blocking of calcium influx, activation of adenosine A1-receptors [6], activation of intracellular signaling cascades such as MAP kinase and Akt, which may lead to changes in gene expression, as well as a direct scavenging of damaging free radicals [7]. In a change of paradigms, the relevance of these specific effects on ischemic cascades is now thought to by far exceed the benefits derived from a simple suppression of cerebral metabolic activity.

Relevance of anesthetic neuroprotection

The degree of protection that can be achieved by anesthetics, as well as the longevity of this effect, remain unclear. Most experimental studies have failed to show a long-term protection by anesthetics, despite impressive short-term protection. In an experimental setup [8] that employs a very mild ischemia regimen, however, protection was still present one month after the insult. This apparent discrepancy may be due to a selective effect of anesthetics on one mode of ischemic cell death only: anesthetic agents may reduce excitotoxic damage by their antagonistic action on NMDA-receptors, suppression of glutamate release, and potentiation of inhibitory activity, thereby decreasing immediate neuronal death. Delayed apoptotic death that takes place long after the anesthetic agent was discontinued may not be affected, however. Alternatively, anesthetics may reduce the severity of the ischemic insult, reducing the number of cells that undergo immediate necrotic death, yet failing to prevent delayed apoptotic suicide of damaged neurons. Either way, the main clinical relevance of neuroprotection by anesthetic agents may be that time is gained and a window of opportunity arises, in which additional means of protection aiming at other elements of the ischemic cascade, such as caspase inhibitors [9,10•], may be applied (multimodal neuroprotection). Beyond a certain threshold of damage severity, however, anesthetics may not be able to protect cells from imminent death [11]. Thus, instead of aiming at complete neuroprotection (reducing the incidence of perioperative stroke), the current approach for anesthetic neuroprotection focuses more on reducing the severity of the insult (reducing morbidity after perioperative stroke).

Timing of anesthetic neuroprotection

Another question that remains to be answered is what timing is best for neuroprotection by anesthetics. Post-insult protection by anesthetics was not easily explained according to the old paradigm of reduction of energy needs by anesthetics, and a clinical study of posttreatment with barbiturates in survivors of cardiac arrest failed to prove beneficial effects. The more modern concept of a specific, receptor-mediated protective action, however, can accommodate protection of the brain from evolving damage after the initial insult, and recent in-vitro studies [12,13•] of posttreatment with anesthetic agents have accordingly supplied promising results. Lasting beneficial effects of previous exposure to anesthetic agents, namely preconditioning, may additionally contribute to improved outcome after cerebral ischemia in the immediate postoperative period. Potential mechanisms involved in this preconditioning effect are currently studied, and may involve adenosine A1 receptor activation [14] and altered gene transcription secondary to changed activation of intracellular signaling cascades [15•].

Tolerability of anesthetic neuroprotection

Reports [16,17] that exposure to anesthetic agents can cause neurodegeneration and cell death, especially in immature brains, have caused new questions about the tolerability of these agents. The discussion focuses on isoflurane, nitrous oxide and ketamine, all of which block the NMDA-glutamate receptor subtype. Interestingly, xenon, also assumed to act via the same receptor system, has not been associated with detrimental effects. Some strongly argue that the reports about anesthetic neurotoxicity in the newborn result from experimental methodology and cannot be easily translated to clinical practice in humans [18••,19,20••]. The relevance of these findings for clinical applications remains uncertain, but further study employing clinically relevant regimens is clearly warranted.

Chiasm between bench and bedside

This discussion emphasizes once more the difficulties encountered when clinical situations are to be modeled in experimental paradigms, and the importance of choosing appropriate controls and outcome measures to achieve meaningful results from experimental studies. Long-term outcome is difficult to study after experimental ischemia, as many models do not permit long-term survival. This is especially true for in-vitro preparations. Appropriate control groups are difficult to establish, as effects of the anesthetic agent on cerebral blood flow and energy consumption before or during ischemia may affect the severity of the insult, which complicates group comparison. In addition, the comparison of results across individual studies is not easy, due to a wide array of different experimental setups, outcome measures used, and time-points studied.

The chiasm between the current lack of clinical evidence of neuroprotection by anesthetic agents in humans and the numerous positive experimental studies results from several factors, which need to be addressed to enable translation from bench to bedside: long-term functional outcome is the single relevant endpoint for patients experiencing cerebral ischemia, yet the vast majority of

experimental studies use short-term follow-up, and assess histopathological endpoints, or even apply in-vitro models of ischemia; dose–response studies are rarely conducted; many models do not adequately depict the clinical reality, that is age, co-morbidity, clinical monitoring, postinsult critical care are not modeled; the pathomechanisms involved in ischemic injury and in neuroprotection by anesthetic agents appear to differ between developing and adult brains, yet many in-vitro models utilize neuronal cells or slices derived from immature animals.

That being said, a number of recent studies on neuroprotection by anesthetics have enhanced our basic understanding of the neuroprotective potential of several anesthetic agents, and of the molecular mechanisms involved in protection.

Isoflurane

Isoflurane may be the one anesthetic receiving most experimental attention. Today, there is a large body of evidence supporting a neuroprotective potential of isoflurane in various experimental models, but the longevity of this effect and the mechanisms behind it remain subjects of intense study.

Acute neuroprotection

Isoflurane protection may be more pronounced against moderate, rather than severe ischemia. Isoflurane at 1% reduced neuronal death in rat hippocampal slice cultures 48–72 h after 60 min of hypoxia, but the protection was lost when hypoxia was maintained for 75 min. The protection required calcium release from intracellular stores, and subsequent activation of MAP kinase and Akt signaling pathways [11]. These signaling cascades may elicit changes in gene expression, as isoflurane exposure (2% for 30 min) was shown to increase expression of heat-shock protein in neuronal/glia co-cultures, while decreasing genes associated with apoptosis [21].

The neuroprotective effect of isoflurane appears to be age dependent, as it is lost in the aging rat. When hippocampal slices derived from 5-day or 23-month-old rats were exposed to oxygen–glucose deprivation (OGD) for 20 min, neuronal injury was more pronounced in the tissue from the older animals, and 1% isoflurane reduced damage in the young, but not the older animal [22•]. Interestingly, isoflurane without OGD resulted in significant neuronal death in slices from older animals. The loss of protection may be related to the failure of isoflurane to limit intracellular Ca^{2+} increase by OGD, or to elicit MAP kinase and Akt signaling in slices from aging animals [22•].

Isoflurane-mediated neuroprotection may only be transient. Hippocampal CA1 neuronal survival 5 days after 10 min of global cerebral ischemia was increased in rats that were anesthetized with isoflurane as opposed to fentanyl/nitrous oxide during ischemia and 2 h of reperfusion [23]. No difference in cell count between the groups was seen 3 weeks or 3 months after the insult, however [23]. This may be due to failure of isoflurane to prevent postischemic apoptosis of damaged neurons. Infarct size was only transiently reduced (on days 1 and 4, but not on day 7) following focal ischemia (MCAO) in isoflurane-anesthetized, as opposed to awake, rats, while apoptotic death was more pronounced in the isoflurane group on days 4 and 7 [24].

Preconditioning

Isoflurane can also been used as a preemptive treatment to increase the tolerance of neurons against a subsequent lethal insult. In a recent study [15•], hippocampal slices exposed to 2 h of 0.5–1.5% isoflurane 24 h prior to OGD exhibited reduced neuronal death 48 h after the insult. This preconditioning effect was associated with Ca^{2+} release from the endoplasmatic reticulum, and depended on calmodulin and MAP kinase signaling.

Isoflurane pretreatment may also influence experimental traumatic brain injury. Isoflurane 1% compared with fentanyl infusion for 30 min before traumatic brain injury in rats was associated with improved functional and cognitive performance 5 days after trauma, while post-treatment after the trauma had no effect [25].

Other volatile anesthetics

Similar to isoflurane, sevoflurane pretreatment recently was shown to induce ischemia tolerance. One MAC of sevoflurane for 30 min applied 15 min before cardiac arrest (acute), or for 30 min on four consecutive days 24 h before arrest (chronic) reduced neuronal death in hippocampal slices harvested 7 days later [26]. The mechanism responsible is unclear, but may involve opening of ATP-dependent potassium channels [26].

Halothane and desflurane have also been shown to possess neuroprotective effects. Both agents reduced infarct size 24 h after 2 h of transient focal cerebral ischemia in rats when applied during ischemia at 1.5 MAC, as compared with the awake state. Infarct reduction by desflurane was more pronounced than by halothane, which was attributed by the authors to a more pronounced decrease in sympathetic tone than can be achieved by desflurane [27].

Xenon

Xenon's anesthetic properties are thought to be mediated in part through NMDA receptor blockade and, accordingly, xenon was shown to have neuroprotective potential [28•]. Seventy percent inhaled xenon during 60 min of focal cerebral ischemia in mice improved neurologic

function and decreased infarct size at 24 h of reperfusion, as compared with 70% nitrous oxide [29]. Xenon can precondition against OGD *in vitro* and against hypoxia/ischemia in neonatal rats by CREB-mediated alteration of gene expression [30•]. Posttreatment with xenon is also effective in reducing neuronal damage. Three hours of 50% inhaled xenon after 90 min of hypoxia–ischemia reduced damage 1 week after the insult in 7-day-old rats [13•]. Subanesthetic doses of xenon add to the neuroprotective effects of hypothermia and appear to favorably affect the ratio of pro compared with antiapoptotic proteins after OGD in neuronal culture as well as after hypoxia–ischemia in neonatal rats [31•].

Barbiturates

While the barbiturates were the first anesthetic agents widely used for perioperative neuroprotection, they became less popular when the focus of the field moved away from protection by reduction of energy consumption to receptor-mediated protection. Although it is now recognized that barbiturates can block glutamate receptors, potentiate GABA-ergic activity and inhibit calcium influx, similarly to other anesthetic agents [32••], there is also strong evidence for a pronounced systemic immunosuppression by barbiturates, which increases the risk of infection [33,34]. This may contribute to the reduced research interest in this group of anesthetics.

Propofol

Propofol at doses resulting in burst-suppression reduced the number of dying neurons and positively affected the ratio of apoptosis-associated proteins following incomplete hemispheric [8]. In this model of mild ischemic injury, neuroprotection was sustained until 4 weeks after the insult [8]. While comparable doses *in vitro* (100 μM) reduced NMDA receptor response in cultured CA1 neurons and hippocampal slices, however, they failed to protect the CA1 region from OGD-induced cell death in a hippocampal slice preparation [35]. The discrepancy between the in-vivo and in-vitro findings is currently best explained by propofol's potential to scavenge free radicals. While neuronal damage from transient cerebral ischemia is in part mediated by free radicals generated during early reperfusion, this mechanism may be less relevant in slice cultures [35]. In contrast to this, however, propofol could reduce infarct size 24 h after permanent middle artery occlusion in rats [36].

No clinical data exist that establish neuroprotection by propofol in humans. A small study [37] comparing propofol compared with isoflurane anesthesia during coronary artery bypass grafting (CABG) in 20 patients found no difference in neuropsychological performance early (days 3–6) after the intervention, and even saw a transient increase in serum S100β levels (a surrogate marker for neuronal damage) in the propofol group.

Ketamine

The neuroprotective potential of ketamine is attributed to its activity as an NMDA-receptor antagonist. A recent in-vitro study [38] showed that 100 μM ketamine during or after 1 h of OGD protected the cellular integrity (reduced LDH release) in striatal slices cultures, although it did not affect neurotransmitter release from these cells. Neuroprotection by ketamine has been described in a variety of different experimental settings, including transient focal and global, as well as permanent ischemia, traumatic brain injury, and in-vitro hypoxia/ischemia. Clinical studies [39••] comparing ketamine sedation with fentanyl or sufentanil after traumatic brain injury, however, failed to find effects on functional outcome after 6 months. Similarly, the addition of S^+-ketamine to propofol/remifentanyl anesthesia during open heart surgery in a clinical study [40] including 106 patients had no effects on neurobehavioral outcome tests one and 10 weeks after the intervention.

Lidocaine

Neuroprotection by lidocaine has been attributed to Na^+-channel blockade. A recent in-vitro study [12] found that postinsult administration of lidocaine to hippocampal slice cultures reduces cell death after OGD. Another study [41] identified a reduction in infarct size 24 h after focal ischemia in rats that was associated with reduced early release of cytochrome c release and caspase-3 activation. Protection of hippocampal slices from OGD was associated with preservation of mitochondrial integrity [42].

Neurotoxic effects of anesthetics

While several lines of clear evidence suggest a distinct neuroprotective potential for various anesthetics, others have reported neurotoxic effects of the very same drugs. NMDA-receptor blockade during synaptogenesis in the immature brain can induce widespread neuronal degeneration [16], and it was suggested that NMDA-antagonistic anesthetics cause cerebral damage in neonates [17]. A recent study [43] on cultured rat forebrain neurons showed evidence of apoptotic cell death and increased expression of bax and the NR1 NMDA receptor subunit after 48 h of ketamine exposure. Ketamine also increased death in nonhuman primate forebrain cultures, which was associated with increased NFkB translocation [44].

Another recent study [18••] adds new evidence to this discussion. Sixty minutes of isoflurane anesthesia (1.8% in oxygen) was found to induce severe hypoglycemia in 10-day-old mice, which was more pronounced after 60 min of hypoxia/ischemia. Isoflurane induced hypoglycemia in newborn mice is an interesting observation, as it may contribute to the neurodegeneration observed in newborn rodents after long-term (6–h) exposure to

volatile anesthetics [17]. These findings emphasize that complete monitoring and control of physiologic parameters, although technically challenging, is a necessary prerequisite if clinically meaningful results are to be obtained from these kinds of experiments [19,20••].

Recent evidence [45] suggests that lidocaine can also exert neurotoxic effects in animal and human spinal cord. This appears to be unrelated to Na^+ channel blockade, but the precise mechanism remains unclear.

Conclusion

Recommending the use of a specific agent for the care of patients at risk for perioperative cerebral ischemia, or in the immediate postinjury period seems premature. Isoflurane appears to be the most promising candidate for a protective agent, but this may be a selection bias, as it is among the most commonly used and studied agents, both clinically and experimentally. Potential negative effects of isoflurane and ketamine in very young and elderly people require more careful study using appropriate, well controlled models. At this point, it seems reasonable to recommend that the anesthesia provider use standard evaluation to choose the anesthetic regimen that is most appropriate for the individual patient, judging by clinical status and co-morbidities. As always, anesthesiologists should strive to provide the best care possible, which may include using techniques they are familiar with, rather than choosing a regimen they are less comfortable with, based on less-than-convincing experimental data.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 579).

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