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Neuroprotective effects of anesthetic agents

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Abstract
Ischemic neuronal injury is characterized by early death mediated by excitotoxicity and by delayed death caused by apoptosis. Current evidence indicates that volatile agents, barbiturates, and propofol can protect neurons against ischemic injury caused by excitotoxicity. In the case of volatile agents and propofol, neuroprotection may be sustained if the ischemic insult is relatively mild; however, with moderate to severe insults, this neuronal protection is not sustained after a prolonged recovery period. This suggests that volatile agents and propofol do not reduce delayed neuronal death caused by apoptosis. The long-term effects of barbiturates on ischemic cerebral injury are not yet defined. Cerebral ischemia is characterized by continued neuronal loss for a long time after the initial ischemic insult. Therefore, in investigations of cerebral ischemia, the duration of the recovery period should be taken into consideration in the analysis of the neuroprotective effects of anesthetic agents. A combination of different approaches that target specific stages of the evolution of ischemic injury may be required for sustained neuroprotection.

Key words Cerebral ischemia · Apoptosis · Isoflurane · Barbiturate · Propofol

Introduction

Cerebral ischemia, although infrequent, is a potentially devastating complication of anesthesia and surgery. The exquisite vulnerability of the brain to cessation of blood flow has fostered a substantial investigative effort to identify pharmacologic agents that might reduce ischemic cerebral injury. Among these, anesthetics have long been considered logical candidates, given their ability to suppress cerebral metabolic rate, to antagonize glutamate-mediated excitotoxicity, and to enhance inhibitory synaptic transmission. Consequently, there is considerable interest in the identification of anesthetic agents that might reduce ischemic neuronal injury. Much of the current investigation has focused on the effects of anesthetics on the pathophysiology of cerebral ischemia, and on their effects on neuronal injury in animal models of cerebral ischemia. The results of these investigations reveal a "good news and bad news" situation [1]. The "good news" is that there is general agreement that volatile agents, barbiturates, and propofol reduce ischemic neuronal injury after a short postischemic recovery period. More recent "bad news" suggests that this neuroprotective effect is not apparent after a long postischemic recovery period. The neuroprotective effect of anesthetics does not appear to be sustained. In this article, we review recent data about the effects of anesthetic agents on ischemic brain injury. We begin with a brief summary of our understanding of the pathophysiology of cerebral ischemia. This is followed by a critical appraisal of the neuroprotective effects of individual anesthetic agents.

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Pathophysiology of cerebral ischemia

Uncontrolled release of glutamate during ischemia and the consequent excessive stimulation of postsynaptic glutamate receptors (excitotoxicity) play a major role in the initiation of neuronal injury (Fig. 1). Depolarization of neurons, mediated by stimulation of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) type of glutamate receptors, results in Na^+ influx and Ca^{++} influx via the voltage-sensitive calcium channel (VSCC). In addition, stimulation of *N*-methyl-D-aspartate (NMDA) receptors leads to intracellular Ca^{++} and Na^+ influx. Excessive intracellular calcium accumulation activates enzymes including proteases, lipases, and endonucleases. Subsequent damage to cellular lipids,

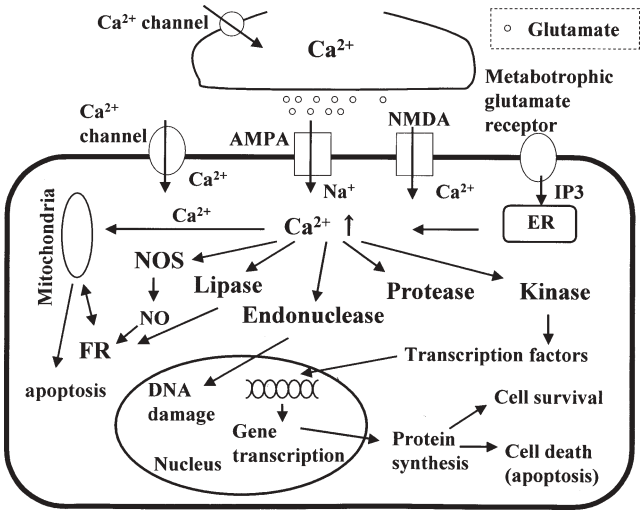

Fig. 1. Possible pathways leading to ischemic neuronal injury. *AMPA*, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid subtype of glutamate receptor; *NMDA*; *N*-methyl-D-aspartate subtype of the glutamate receptor; *IP3*, inositol 1,4,5-triphosphate; *ER*, endoplasmic reticulum; *NOS*, nitric oxide synthase; *NO*, nitric oxide; *FR*, free radical

proteins, and DNA leads to free radical production, membrane lipid breakdown, and proteolysis, which ultimately leads to neuronal death within a short time after the onset of ischemia. Excitotoxic neuronal death is characterized by neuronal swelling, nuclear pyknosis, acidophilic cytoplasm, and finally, cell lysis.

The role of excitotoxicity in ischemic neuronal injury is widely acknowledged. Indeed, glutamate antagonists of both NMDA and AMPA receptors have been shown to be neuroprotective in global and focal cerebral ischemia [2–4]. More recent data, however, indicate that this neuroprotective efficacy is not sustained. For example, NMDA antagonists were able to reduce neuronal injury when injury was evaluated after a short recovery period (3 days); however, when injury was evaluated 4 weeks after ischemia, this neuroprotection was not apparent [5]. The work of Du et al. [6] has indicated that ischemic injury is a dynamic process characterized by ongoing neuronal loss for at least 14 days (and probably longer) after ischemia. This delayed neuronal death occurs at a time when glutamate concentrations are at their basal levels; therefore, processes other than excitotoxicity probably lead to delayed neuronal death. Du et al. [6] proposed that this delayed death is caused by apoptosis.

The role of apoptosis in the development of ischemic neuronal death has been confirmed by a number of investigations. Neuronal apoptosis, detected by terminal deoxynucleotidyl transferase-mediated dUTP-biotin in situ nick labeling (TUNEL) staining and DNA laddering, occurs early during ischemia [6,7]. Although the mechanism by which apoptosis is triggered is not clear, signaling pathways of ischemia-induced apoptosis may include intrinsic (mitochondria-mediated), extrinsic (receptor-mediated), and caspase-independent pathways (Fig. 2) [8]. The intrinsic pathway is characterized by cytochrome *c* release from mitochondria, which leads to procaspase 9 cleavage and activation. This ultimately results in activation of effector caspases, including caspase 3 [9–11]. The extrinsic pathway is characterized by activation of cell death receptors initiated by their ligands [e.g., FasL, tumor necrosis factor-α (TNF-α)], which leads to cleavage of procaspase 8. Cleaved caspase 8 then activates downstream caspases and results in apoptosis [11–13]. In fact, the administration of caspase inhibitors has been reported to reduce neuronal injury after cerebral ischemia [14,15]. By contrast, apoptosis-inducing factor (AIF), which is released from the mitochondria, is also thought to be an important candidate responsible for apoptosis via caspase-independent pathways [8]. Collectively, these data indicate that a substantial proportion of neuronal death is caused by apoptosis.

From the foregoing discussion, it is quite clear that in analysis of the protective effect of anesthetic agents, the duration of the recovery period (the time at which the extent of injury is evaluated) must be taken into consideration. A reduction in injury by a given agent after a short recovery period may not be apparent after a longer recovery period, i.e., neuroprotection is not sustained.

Inhalational anesthetics

A number of investigators have demonstrated that volatile anesthetics can reduce ischemic cerebral injury. Warner et al. [16] demonstrated that both halothane and sevoflurane substantially reduced the volume of infarction after focal ischemia compared with that in the awake state. Miura et al. [17] demonstrated that hippocampal CA1 injury and cortical injury after near-complete global ischemia were less in rats anesthetized with isoflurane compared with those receiving ketamine or nitrous oxide and fentanyl. Soonthon-Brant et al. [18] have also shown that infarct volume after focal cerebral ischemia in rats anesthetized with isoflurane was significantly lower than that in animals that were either awake or sedated with fentanyl.

The precise mechanism by which volatile anesthetics reduce brain injury is not clearly defined. A number of investigators have indicated that volatile anesthetics can attenuate excitotoxicity by inhibiting glutamate release and postsynaptic glutamate receptor-mediated responses. Beirne et al. [19] examined the effect of hal-

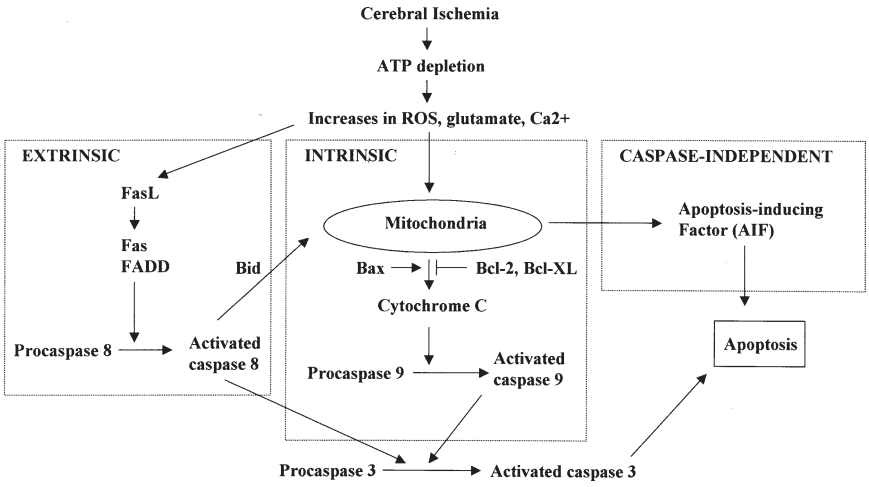

Fig. 2. Signaling pathways of ischemia-induced apoptosis, including intrinsic (mitochondria-mediated), extrinsic (receptor-mediated), and caspase-independent pathways. Apoptotic insults lead to cytochrome *c* release from the mitochondria into the cytoplasm, which forms the apoptosome consisting of Apaf-1 and procaspase 9 and then activate caspase 9. This ultimately results in activation of caspase 3. The release of cytochrome *c* is regulated by proapoptotic proteins Bax and antiapoptotic proteins Bcl-2 and Bcl-XL. The death receptor pathway is triggered by the binding of Fas ligand (*FasL*) to Fas, which activates caspase 8 via Fas-associated death domain protein (*FADD*). A number of different cell receptors and their ligands can be involved in this process. Activated caspase 8 then activates caspase 3 and can also interact with the intrinsic pathway by activating proapoptotic protein Bid. A caspase-independent pathway also exists in which apoptotic-inducing factor is released from the mitochondria and directly causes chromatin condensation and DNA cleavage. *ROS*, reactive oxygen species

othane on NMDA-mediated excitotoxicity in primary neuronal culture and indicated that halothane was found to antagonize NMDA excitotoxicity. Isoflurane has been shown to reduce excitotoxic injury mediated by NMDA and AMPA in vivo in rats [20,21]. Isoflurane can also reduce the frequency of spreading depression-like transient depolarizations during focal ischemia [22]. These depolarizations increase calcium influx into neurons, thereby augmenting neuronal injury. Inhibition of these depolarizations by isoflurane can limit injury caused by focal ischemia. In addition, Bickler et al. [23] recently reported that isoflurane neuroprotection in organotypic hippocampal cultures involves γ-aminobutyric acid-A (GABA-A) receptors. The influence of anesthetics on sympathetic tone also has been proposed as a possible mechanism of volatile anesthetic-mediated neuroprotection. Mackensen et al. [24] investigated the relationship between the adrenergic response and histologic outcome from near-complete forebrain ischemia in rats. Isoflurane attenuated the peripheral sympathetic response to ischemia and improved histologic outcome compared with fentanyl and nitrous oxide. However, this benefit was reversed by sympathetic ganglionic blockade, indicating that beneficial effects of isoflurane may result from a partial blockade of the sympathetic response.

In most of the investigations of anesthetic-mediated neuroprotection, the extent of neurologic injury was evaluated after only short recovery periods (up to 7 days) after ischemia. However, as mentioned previously, ischemic neuronal loss can continue for a long time after ischemia. Kawaguchi et al. [25] investigated the long-term effect of isoflurane on ischemic injury after focal cerebral ischemia in rats. In comparison with an awake control state, 1.5 MAC of isoflurane substantially reduced the extent of infarction 2 days after focal ischemia. However, the infarction-sparing effect was not apparent after a 2-week recovery period, indicating that isoflurane delays, but does not prevent, infarction caused by focal ischemia. Elsersy et al. [26] recently reported that rats anesthetized with isoflurane had less neuronal injury 5 days after forebrain ischemia compared with those receiving fentanyl–nitrous oxide, but this neuroprotective efficacy of isoflurane was not observed at 3 weeks and 3 months after ischemia.

Although the mechanisms that underlie the progression of injury in the ischemic brain have not been clarified, neuronal apoptosis can play an important role. Kawaguchi et al. [27] investigated the effects of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia and demonstrated that the increase in size of cerebral infarction in isoflurane-treated animals parallels the appearance of markers of apoptosis such as TUNEL and caspase 9- and caspase 3-positive cells. In addition, Inoue et al. [28,29] investi-

gated the effects of combination of isoflurane (during ischemia) and caspase inhibitors (every 24 h for 14 days) on neuronal injury in rats subjected to focal ischemia. They demonstrated that the broad spectrum caspase inhibitor zVAD-fmk and the caspase 8 inhibitor IETD-fmk prevented infarct extention in isoflurane-treated animals and that sustained neuroprotection over 14 days was observed when isoflurane was combined with these caspase inhibitors. These data suggest that prevention of apoptosis may be a target for future interventions for long-term neuroprotection.

In contrast, the work of Engelhard and colleagues has shown that volatile agent-mediated neuroprotection is sustained even 4 weeks after ischemia [30]. In a model of hemispheric ischemia combined with hemorrhagic hypotension, sevoflurane was remarkably effective in preventing neuronal death in the hippocampus. A closer examination of the data of Engelhard et al. may provide an explanation for the apparent discrepancies between their results and those of other investigators. In the study of Engelhard et al. [30], the severity of the ischemia was such that in the control nonanesthetized group, injury was relatively mild. Remarkably, no injury was detected in the sevoflurane-anesthetized group. These data indicate that the ischemia-inducing insult was relatively mild in comparison to the severity of insult in other investigations. Therefore, a reasonable explanation for these results is that volatile agent-mediated neuroprotection can be sustained *if the ischemic insult is mild*; with moderate to severe insults, volatile agents are not able to effect long-term protection of the brain.

Barbiturates

There have been a number of demonstrations of the protective efficacy of barbiturates on outcome from permanent and transient focal cerebral ischemic insults in a variety of animal models [31–37]. The majority of animal studies have clearly demonstrated the neuroprotective efficacy of barbiturates administered before, during, or after focal ischemia, although comparable results in humans are lacking. In contrast, the neuroprotective efficacy of barbiturates on outcome from global ischemia is controversial [38–45]. Initial reports from animal models of global ischemia demonstrated that barbiturates administered before, during, or after cardiac arrest improved neurological outcome, whereas subsequent studies failed to show neuroprotective efficacy of barbiturates in models of global ischemia. A recent report by Amakawa et al. [45] demonstrated that thiopental administered before or after forebrain ischemia reduced neuronal damage in gerbils, although treatment with thiopental after ischemia required a larger dose than that before ischemia. In humans, however, a randomized clinical study in comatose survivors of cardiac arrest showed no beneficial effect of thiopental loading on neurological outcome compared with those receiving standard therapy [46].

The neuroprotective effect of barbiturates was initially attributed to their ability to reduce cerebral metabolism; however, a critical appraisal of the available literature indicated that metabolic depression does not appear to play a significant role in anesthetic-mediated neuroprotection. Warner et al. [47] first demonstrated that the reduction in infarct volume in rats subjected to focal ischemia was similar whether pentobarbital was administered in EEG-burst-suppression doses or in doses approximately one-third of that required to produce EEG burst suppression. These data were confirmed in a similar study conducted by Schmid-Elsaesser and colleagues [48]. Another interesting finding is that electrophysiologically comparable doses of the various classes of barbiturates (i.e., thiopental, methohexital, and pentobarbital) can have different neuroprotective efficacy in a model of focal ischemia, suggesting that mechanisms other than, or at least in addition to, metabolic suppression may contribute to the protective effect of barbiturates [49].

Barbiturate-mediated neuroprotection has been attributed to redistribution of cerebral blood flow to injured areas, Na-channel and glutamate receptor blockade, inhibition of calcium influx, inhibition of free radical formation, and potentiation of GABA-ergic activity. Zhu et al. [50] demonstrated that thiopental attenuated NMDA- and AMPA-mediated glutamate toxicity in hippocampal slices in vitro. Kimbro et al. [20] have also shown that pentobarbital can reduce AMPA excitotoxicity in vivo in rats. In addition, thiopental was found to attenuate ischemia-induced intracellular calcium increases in the hippocampus and cortex [51]. These effects were attributed to a thiopental-mediated inhibition of both VSCC and NMDA receptors. Pentobarbital can also reduce the frequency of transient ischemic depolarizations during focal ischemia [52]. This mechanism might also contribute to the neuroprotective effect of barbiturates. Barbiturates can act as a free-radical scavenger to protect the neurons in the brain. Shibuta et al. [53] demonstrated that thiopental, but not pentobarbital, protected both cortical and hippocampal primary cultured neurons from nitric oxide-induced cytotoxicity in a dose-dependent manner.

In most studies to date, the neuroprotective efficacy of barbiturates has been evaluated after only a short recovery period. Whether barbiturate-mediated brain protection is sustained is not known. This is an important issue that needs experimental clarification.

Propofol

It has been suggested that propofol is an ideal anesthetic for neurosurgery because of its presumed beneficial effects on cerebral physiology (a reduction in cerebral metabolic rate, a reduction in cerebral blood flow, and brain relaxation). Laboratory investigations have also revealed that propofol might also protect the brain against ischemic injury. Young et al. [54] reported that infarct volume in rats anesthetized with propofol was significantly less than that in isoflurane-anesthetized animals. Pittman et al. [55] demonstrated that neurologic and histologic outcome were similar in pentobarbital- and propofol-anesthetized rats subjected to focal ischemia. Given that pentobarbital is considered to have neuroprotective properties, these data indirectly indicate that propofol can also reduce ischemic injury. Ito et al. [56] examined the effect of propofol on neuronal damage induced by forebrain ischemia in gerbils and indicated that neuronal injury in the hippocampal CA1 and parietal cortex was significantly attenuated by propofol administration. Gelb et al. [57] reported that propofol administration for a period of 4 h, initiated immediately and 1 h after focal ischemia, significantly reduced infarct volume compared with that in the awake control rats.

The neuroprotective effect of propofol has been attributed to its antioxidant properties, its potentiation of GABA-A-mediated inhibition of synaptic transmission, and its inhibition of glutamate release. Propofol has been reported to directly scavenge free radicals and to decrease lipid peroxidation [58]. Yamaguchi et al. [59] reported that propofol attenuated delayed neuronal death by preventing lipid peroxidation induced by transient forebrain ischemia in the hippocampal CA1 subfield in gerbils. Sitar et al. [60] indicated that propofol can prevent and reverse peroxide-induced inhibition of excitatory amino acid uptake (glutamate transport) in cultured astrocytes. These findings suggest that neuroprotection by propofol might be a reflection of a direct scavenging effect against reactive oxygen species generated during the ischemia and reperfusion. Ito et al. [56] demonstrated that pretreatment with the GABA-A antagonist bicuculline significantly inhibited the neuroprotective effects of propofol in a gerbil model of forebrain ischemia, suggesting a role for GABA-A receptors in propofol-induced neuroprotection. Engelhard et al. [61] demonstrated that cerebral glutamate concentration was decreased by 60% with propofol compared with nitrous oxide/fentanyl anesthesia in rats subjected to forebrain ischemia.

In the foregoing studies, neurologic assessment was performed after only a short recovery period (up to 7 days). Recently, Bayona et al. [62] showed that propofol infusion decreased infarction volume 3 days after insult in an endothelin-induced striatal ischemia model. However, when the animals were evaluated 3 weeks after ischemia, no difference between propofol-treated or control animals could be detected histologically. In this regard, the neuroprotective efficacy of propofol is similar to that of isoflurane: propofol delays, but does not prevent, cerebral infarction after focal ischemia. In contrast, Engelhard et al. [63] investigated the effect of propofol on neuronal damage and key proteins of apoptotic cell death in a model of hemispheric ischemia combined with hemorrhagic hypotension. They demonstrated that propofol, compared with nitrous oxide and fentanyl, reduced neuronal damage and favorably modulated apoptosis-regulating proteins for at least 28 days, suggesting long-term neuroprotection by propofol. As mentioned above, the severity of ischemia in this model was, however, relatively mild so that no injury was detected in the propofol-anesthetized group. These results may suggest that propofol, as well as volatile agents, may be neuroprotective over a long postischemic recovery period if the ischemic insult is mild, but that propofol-mediated neuroprotection is not sustained with moderate to severe insults.

Conclusion

The available data indicate that barbiturates, volatile anesthetics, and propofol can reduce ischemic cerebral injury (Fig. 3). The effects of these agents appear to be

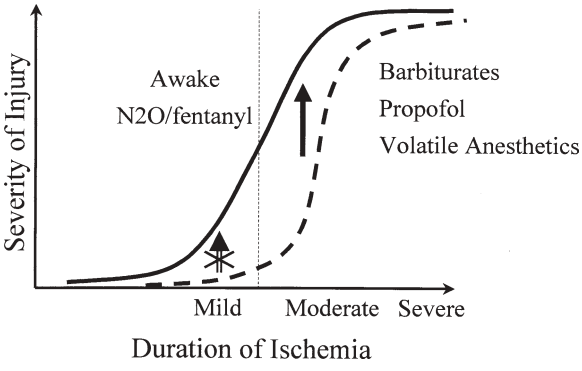

Fig. 3. A summary of relationships between the duration of ischemia and severity of injury in cerebral ischemic models. After a short recovery period (usually less than 4 days), barbiturate, propofol, and volatile anesthetics can be neuroprotective (*dashed line*) compared with awake and nitrous oxide (N_2O)/fentanyl anesthesia (*solid line*). However, neuronal injury in animals anesthetized with barbiturate, propofol, and volatile anesthetics can increase over a longer recovery period (usually more than 14 days, *arrow*) if ischemic injury is moderate or severe. If ischemic injury is mild (brief), such maturation of neuronal injury may not be observed (*open arrow*). Sustained anesthetic neuroprotection may therefore be limited to brief ischemia

directed primarily against excitotoxic injury. The long-term effects of barbiturates on postischemic neurons are currently not known. In the case of volatile agents and propofol, neuroprotection may be sustained if the ischemic insult is relatively mild. If, however, the injury is such that some neuronal injury occurs under anesthesia, then the reduction in injury may not be sustained. These agents delay the development of cerebral injury but do not prevent it. However, by delaying the development of injury, volatile agents and propofol can increase the therapeutic window for the application of other agents directed against apoptosis. Considering that the pathophysiology of cerebral ischemia is complex and that a number of diverse processes are initiated by the ischemic insult, a single pharmacologic intervention is unlikely to result in sustained neuroprotection. A combination of different approaches that target specific stages of the evolution of ischemic injury may be required.

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