Anesthetics and Cerebroprotection: Experimental Aspects

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Early observations in patients under general anesthesia set the stage for the concept that anesthetic agents could also serve to protect the brain from an ischemic or hypoxic insult [1]. Anesthetics may affect ischemic or traumatic brain injury by numerous mechanisms, and their potential for cerebroprotection and brain resuscitation is clinically relevant. In designing the anesthetic plan for patients at high risk of cerebral ischemia (e.g., carotid endarterectomy, open-heart procedures), it is useful to consider the relative degree of protection provided by various agents. Similarly, treating patients with an anesthetic after cardiac arrest or a focal ischemic insult may be a consideration in improving overall neurological outcome. Much of our knowledge surrounding anesthetics and cerebroprotection originates from animal studies in which outcomes following cerebral ischemia have been compared with different anesthetic regimens. Typically, the protective properties of anesthetic agents have been compared as pretreatments in the presence of an accompanying baseline anesthetic. Relatively few data are available that compare outcomes when administering the anesthetic only after the onset of ischemia/reperfusion or comparing outcomes in awake animals who are free of potentially confounding baseline anesthetic agents.

In interpreting cerebroprotection studies, it is important to characterize the experimental model of ischemia by the magnitude, duration, and distribution of cerebral blood flow (CBF) reduction. By definition, global cerebral ischemia affects whole brain, but CBF reduction may be complete (zero blood flow) or incomplete. Studies of incomplete ischemia can be of special interest if they mimic clinically relevant brain insults. However,

these findings can also be difficult to evaluate if CBF is not measured, because various models and experimental paradigms produce different levels of residual blood flow and target-cell injury. Rodent models of global forebrain ischemia are commonly employed because of their simplicity and because they preserve brain stem blood flow and respiratory and cardiovascular stability. Global forebrain blood flow (i.e., to cortex, striatum, hippocampus) is severely reduced (0–5 ml/min/100 g) in these models. Finally, focal ischemic models are employed to study stroke (e.g., middle cerebral artery occlusion that produces a spatial blood flow gradient from core to periphery). The period of occlusion is usually several hours in order to produce consistent infarction. In permanent stroke models, the occlusion is not reversed. In contrast, many experimental approaches incorporate transient, or reversible, focal models in which occlusion is followed by reperfusion.

The purpose of this chapter is to evaluate the cerebroprotective or resuscitative potential of commonly used anesthetics from data obtained in experimental systems. Relevant studies that provide clues to the mechanisms of anesthetic action in brain injury are discussed. Lastly, the effect of each agent on CBF and cerebral oxygen consumption ($CMRO_2$) is summarized because these variables may directly impact ischemic outcomes in vivo.

■ Barbiturates

Protective Effects in Cerebral Ischemia

The first studies to evaluate efficacy of barbiturates in the setting of global cerebral ischemia found them to be of great therapeutic value. In these studies, the duration of ischemia required to produce severe alteration in the neurological examination was much greater in animals treated with barbiturates as compared to animals studied under local or very light levels of alpha-chloralose anesthesia [2–4]. However, these studies were flawed in that the control group of animals were subjected to significant surgical intervention and ischemia with minimal anesthesia and were likely to have very high baseline catecholamine levels. These factors may have negatively impacted ischemic tolerance in the control animals [5, 6].

Further optimism about the potential clinical utility of barbiturates as a therapeutic modality in the setting of global cerebral ischemia came from a study in primates [7]. This led one group to design a study of barbiturate efficacy in patients following cardiac arrest [8]. However, other laboratories, with better controlled experimental designs, were unable to confirm any beneficial effects of barbiturates with transient global ischemia in dog [9, 10] or cat [11] models. In addition, subsequent attempts to repeat the initial positive results in a primate model of transient global

ischemia were unsuccessful [12]. It was, therefore, not surprising that the randomized clinical trial of thiopental loading in comatose survivors of cardiac arrest did not support the use of thiopental for brain resuscitation [13].

The possible utility of barbiturates in the setting of focal ischemia was first addressed by Yatsu and colleagues [14], and many subsequent studies have demonstrated a therapeutic role for barbiturates [15–20]. However, several issues remain unresolved. First, part of the benefit associated with barbiturate treatment may be related to the drug's ability to decrease brain temperature [21]. Second, it is not clear if barbiturates are as protective in permanent focal ischemia as in transient occlusion [22]. Clinical studies employing barbiturates for brain protection have shown mixed results in acute stroke and cerebrovascular surgery [23–25]. The most convincing evidence for efficacy of barbiturates has been reported in patients with focal brain injury following open-heart surgery and warm cardiopulmonary bypass [26]. Although some concern has been expressed concerning the validity of this study [27], it was the first randomized study in humans that demonstrated improved outcome resulting from barbiturate therapy [28].

Therefore, barbiturates do not provide protection following transient global ischemia but do protect the brain from injury when administered in specific models of focal ischemia. Although the mechanism of protection is unknown, it is likely to be multifactorial.

Potential Mechanisms

Numerous studies document the depressant effect of barbiturates on both CBF and $CMRO_2$ in many species, including man [29, 30]. These agents do not alter CBF autoregulation [31]; however, the response to hypoxia [31] and hypercapnia is attenuated as a function of metabolic depression [32, 33]. The mechanism of metabolic depression is unknown but is thought to be related to enhanced γ-aminobutyric acid (GABA) binding and consequent increased intracellular chloride ion flux [34]. Early studies in cerebroprotection suggested that barbiturate-associated protection is mediated via reduced metabolic demand [35]. Greatest efficacy has been observed in paradigms in which electroencephalographic (EEG) activity remains present during the ischemic period (e.g., focal ischemia), whereas little efficacy is present when the EEG is ablated during ischemia (e.g., complete transient global ischemia). Nevertheless, the metabolism hypothesis has not been substantiated because subsequent findings suggest that reduction of cerebral metabolism does not necessarily result in cerebral protection [36, 37].

Barbiturates may also have direct effects on vascular tone that could affect ischemic outcomes. In isolated cerebral arteries, thiamylal and thio-

pental, but not pentobarbital, produce dose-related contraction. However, these effects are not consistently observed in pial vessels in situ [32]. Under basal conditions, CBF is lower in animals anesthetized with pentobarbital as compared to halothane or fentanyl [38]. Although blood flow can be similarly reduced during middle cerebral artery occlusion regardless of anesthetic, postischemic hyperemia is much more robust in cats anesthetized with pentobarbital as compared to halothane or fentanyl [38]. The therapeutic implications of accentuated postischemic hyperemia with pentobarbital anesthesia remain unevaluated. Barbiturates also decrease agonist-induced cerebral vasoconstrictor responses [39–41], either by blocking calcium entry into vascular smooth muscle [42] or by inhibiting protein kinase C activation [43, 44]. Although reduction in CBF may be important in the mechanism of brain protection from head trauma with elevated intracranial pressure (ICP), it does not appear important in ischemic mechanisms [45].

Numerous studies have demonstrated that intracellular calcium increases during ischemia, activating phospholipases and liberating free fatty acids such as arachidonic acid [46, 47], with consequent amplification of prostanoid production and brain injury. Barbiturates could be of therapeutic value because these agents decrease the production of free fatty acids during ischemia [48]. However, barbiturates do not attenuate accumulation of prostanoids during reperfusion [49].

Although some barbiturates act as free radical scavengers, this is not a property of all barbiturates purported to have therapeutic efficacy in the setting of ischemia. For example, phenobarbital, pentobarbital, and methohexital do not act as oxygen radical scavengers [50]. Godin and associates [51] hypothesized that barbiturate protection may be related to stabilization of hemocoordinated iron complexes in red blood cells with decreased radical production. Leukocytes are also important as generators of oxygen radicals during reperfusion. Therefore, barbiturates may indirectly reduce oxygen radical production by virtue of depressing leukocyte function [52].

Many insults, including ischemia, hypoxia, hypoglycemia, and head trauma, have been demonstrated to cause accumulation of excitatory amino acids (e.g., glutamate, aspartate) in brain [53–55] that directly mediate neurotoxicity and neuronal loss. Barbiturates have been found to be potent antagonists of excitatory amino acid receptors in vitro [56–58]. This is important because glutamate receptor antagonists reduce neuronal injury and histopathology associated with focal ischemia [59–61].

In summary, barbiturates appear to be protective in the setting of focal and incomplete, but not complete, global cerebral ischemia. It is not clear why barbiturates do not decrease brain injury in subjects exposed to transient complete global ischemia. The mechanism of protection during focal

ischemia may be due to decreased production of free fatty acids during ischemia [48] or inhibition of excitotoxic mechanisms [56–58].

■ Inhalational Anesthetics

Neuroprotection During Ischemia/Reperfusion

The first inhalational anesthetic to be considered a neuroprotectant was cyclopropane when used in patients undergoing temporary carotid artery occlusion [1]. Subsequent work compared halothane to pentobarbital. Several authors reported improved neurological outcome after middle cerebral artery occlusion in pentobarbital anesthetized animals as compared to halothane anesthesia [15, 17]. Michenfelder and Milde [17] reported significant species dependence in these outcomes.

As isoflurane was employed commonly in the 1970s and 1980s, its role as a possible cerebral protectant was evaluated. Initial studies indicated that it could prolong survival time in mice subjected to severe hypoxia and slow the development of ischemic metabolic changes in dogs exposed to severe hypotension [62]. In primates exposed to temporary focal ischemia, isoflurane produced a similar degree of neuroprotection as thiopental [63, 64]. Consistent with a neuroprotective role of isoflurane, retrospective analysis of data from the Mayo Clinic indicates that isoflurane-anesthetized patients demonstrated fewer ischemic EEG changes during carotid surgery than patients anesthetized with enflurane or halothane [65]. In addition, the ischemic threshold (the CBF at which ischemic EEG changes occur) was higher in halothane-anesthetized patients as compared to patients anesthetized with isoflurane [66]. Data from animal studies indicate that the ischemic threshold with isoflurane is greater than that of methohexital [67] but not different from halothane [68].

Although initial studies suggested an advantage of isoflurane and barbiturates over halothane as neuroprotectants, subsequent well-controlled animal studies revealed a similar degree of protection for each of these three agents [20, 69–71]. Likewise, the degree of neuroprotection produced by halothane is similar to that produced by a new inhalational anesthetic, sevoflurane [72]. It is now apparent that the protective effects of halothane can be best appreciated in experimental paradigms that allow strict control over brain temperature [73]. This observation is important because the degree of neuroprotection provided by mild hypothermia (temperature reduction of 3° C) is far greater than that provided solely by inhalational anesthetics [36].

In summary, inhalational anesthetics (isoflurane, halothane, and sevoflurane) reduce brain injury in animal models of focal or incomplete ischemia by mechanisms that are not presently understood. In the sections that

follow, the vasodilator effects of the inhalational anesthetics are explored to gain clues to their potential neuroprotective mechanisms.

Vasodilator Mechanisms

Inhalational anesthetics cause an increase in CBF in vivo [74–77] and vasodilation of cerebral blood vessels in vitro [78, 79]. The cerebral hyperemic response is only transient in subprimate mammals [80], but we have recently found it to be sustained in primates [81]. Increased CBF is accompanied by a decrease in $CMRO_2$ and consumption of glucose [75, 82], but high-energy phosphate metabolism is maintained [83]. The decrease in $CMRO_2$ is linked to a decrease in EEG activity and plateaus once the EEG becomes isoelectric [84]. Because these agents both increase CBF and decrease brain metabolism, it is unlikely that the vasodilation is metabolically mediated. Desflurane, a new inhalational anesthetic, also produces an increase in CBF and decrease in $CMRO_2$ that is similar in magnitude to the other potent inhalational anesthetics [85]. Many different mechanisms have been suggested for the vasodilation associated with inhalational anesthetics, including nitric oxide production, which is also implicated in the cellular basis of ischemia injury.

Nitric Oxide Under baseline pentobarbital anesthesia, inhibition of nitric oxide synthase (NOS) prevents cerebral hyperemia to halothane, isoflurane, and nitrous oxide in dogs [86]. This effect is reversible by L-arginine administration, further supporting a direct role of NO in the mechanism of isoflurane-induced cerebral hyperemia [87]. Others have found that NO is an important mediator of halothane-induced cerebral vasodilation in pial vessels [88]. The source of NO production may be perivascular nerves [89], astrocytes [90], and/or parenchymal neurons [91]. The role of NO in the mechanism of ischemia-induced brain injury is controversial, and ischemic outcomes are best interpreted by keeping in mind which isoforms of NOS (e.g., endothelial vs neuronal) are inhibited in the experimental paradigm. Several laboratories have demonstrated that NOS inhibition results in improved outcome from focal ischemia [92, 93]. However, others have suggested that inhibition of NO production may increase brain injury because of accentuated CBF reduction and that administering L-arginine (inferentially increasing NO production) may decrease brain injury [94, 95]. Therefore, if inhalational anesthetics alter brain NO, then they could also alter ischemic injury by a NO-mediated mechanism.

Prostanoids Indomethacin prevents aortic vasodilation produced by halothane, enflurane, and isoflurane in vitro, suggesting that prostanoids may be important in the mechanism of inhalational anesthetic-induced vasodilation [96]. In vivo prostanoids clearly play an important role in

the mechanism of isoflurane-induced vasodilation [87]. For example, indomethacin markedly attenuates isoflurane induced vasodilation [87]. Whether increased prostanoid production is important in the cerebroprotection associated with inhalational anesthetics is unclear. Increased levels of prostanoids have been implicated as detrimental in ischemia, yet vasodilator prostanoids may facilitate better recovery of CBF during postischemic reperfusion. Further, any effect of prostanoids to increase cyclic adenosine monophosphate (cAMP) levels in brain may be associated with improved recovery from cerebral ischemia [97].

Excitatory Amino Acids Another potential mechanism for inhalational anesthetic–induced cerebral hyperemia and amelioration of ischemic brain injury involves the excitatory neurotransmitter, glutamate. Several inhalational anesthetics have been demonstrated to have important interactions with the N-methyl-D-aspartate (NMDA) class of glutamate receptors. Enflurane inhibits glutamate binding at the NMDA receptor, probably by interacting with the glycine recognition site [98]. Similarly, halothane, isoflurane, and methoxyflurane all disturb glutamate transmission in vitro, both at the glutamate binding site and via receptor-channel activation mechanisms [99]. In addition, isoflurane significantly reduces L-glutamate and NMDA-mediated intracellular calcium fluxes [100]. These actions suggest that the inhalational anesthetics could inhibit ischemic injury mediated via glutamate toxicity. However, not all data support such a role. For example, neither halothane nor isoflurane affect the release of glutamate or glycine during global cerebral ischemia [101]. In fact, halothane and enflurane increase glutamate release from cortical synaptosomes [102].

In summary, under controlled experimental conditions, inhalational anesthetics provide a degree of neuroprotection that is qualitatively similar to that provided by barbiturates in the setting of focal or incomplete ischemia. The mechanism of neuroprotection is unknown but may be related to nitric oxide synthesis, prostanoid production, or disruption of glutamate neurotransmission.

■ Nitrous Oxide

There are inconsistencies among studies regarding the degree of neuroprotection provided by barbiturates in animal models of ischemia. Some authors have speculated that the reason for the discrepancy is the inconsistent use of nitrous oxide. In general, barbiturates have limited efficacy as cerebral protectants in studies that employed nitrous oxide as part of the anesthetic management. However, barbiturates were efficacious in those studies that did not employ nitrous oxide as part of the anesthetic management [103].

The question of whether nitrous oxide is detrimental to neurological outcome following either focal or global ischemia has never been directly evaluated. However, two studies have addressed the effects of nitrous oxide on anesthetic-induced neuroprotection in the setting of transient focal ischemia. Nitrous oxide decreases isoflurane's efficacy as a neuroprotectant [104], but this is not the case for barbiturates [105]. The authors' hypothesize that nitrous oxide attenuates isoflurane-induced neuroprotection by increasing cerebral metabolism [104]. In contrast, metabolism would be maximally reduced with large doses of barbiturates and potentially unresponsive to nitrous oxide administration [105].

Nitrous oxide causes a mild degree of cerebral vasodilation via a mechanism that involves activation of NOS [86]. The effect of nitrous oxide, alone, on neurological ischemic tolerance is not known. When it is administered alone, for surgery, it does not provide adequate anesthesia and is associated with high systemic catecholamines. The high systemic catecholamine state, in turn, would be expected to result in worsening of neurological outcome following cerebral ischemia [69, 104]. Nitrous oxide may attenuate the protective effects of other anesthetics when these other agents are administered at low levels.

■ Ketamine

Ketamine is a noncompetitive NMDA-receptor antagonist [106] that inhibits agonist-induced calcium ion influx. It also attenuates the systemic catecholamine response that normally occurs during incomplete forebrain ischemia [107]. Ketamine has only been evaluated as a neuroprotectant in the setting of focal or incomplete ischemia. In a gerbil model, ketamine increased the incidence of cerebral infarction during carotid ligation relative to pentobarbital [108]. However, lack of control of brain temperature during anesthesia and surgery may have biased these results. In rat, some [107, 109] but not all studies [110, 111] demonstrate that high-dose ketamine can protect the brain following incomplete forebrain ischemia or transient focal ischemia [111]. The mechanism of protection for ketamine may relate to its properties as an NMDA-receptor antagonist or its ability to attenuate systemic catecholamine release.

■ Etomidate

Etomidate (1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid ethyl ester) decreases CBF and $CMRO_2$ without altering blood pressure [112]. Although the mechanism for the reduction in CBF is believed to be due to a reduction in $CMRO_2$, this has not been proved. Etomidate is used widely for neuroprotection [113] because of its low incidence of hemody-

namic instability at doses sufficient to depress the EEG [114, 115]. The agent attenuates ischemia-induced dopamine release in the corpus striatum in rat [116]. Pretreatment with etomidate doubles the time to EEG isoelectricity in response to intravenously administered potassium cyanide [117] and decreases brain injury following a transient focal ischemic/anoxic insult (Levine preparation) in rats [118]. In moderate incomplete global ischemia (significant residual EEG activity present during insult), etomidate delays the loss of cerebral high-energy phosphates and accumulation of brain lactate [119]. This effect presumably is due to drug-induced depression of cerebral metabolism [120], thereby decreasing substrate need at a time of decreased substrate availability. At equally potent doses (doses that produced full ablation of EEG), etomidate and thiopental produce similar neuroprotection in a model of severe forebrain ischemia in rat [121].

Therefore, etomidate is an effective therapeutic agent to prevent brain injury in focal or incomplete ischemia (i.e., like barbiturates, it requires residual neuronal activity for efficacy). Although etomidate has a major advantage over thiopental in that etomidate does not cause hemodynamic instability at a dose that causes maximal reduction in EEG activity, it is associated with significant adrenocortical suppression, even when administered as a single injection [122]. The drug's effect on adrenocortical function has greatly limited its utility in routine anesthetic care but not its utility in neurosurgical cases in which patients are routinely administered high doses of steroids.

■ Opiates

At clinically relevant doses, the effect of opiates on CBF is limited and linked to a reduction in $CMRO_2$. However, some agents have indirect effects that independently affect CBF; for example, morphine causes release of histamine [123] with the potential for cerebral vasodilation. Opiates may also alter CBF because they inhibit release of acetylcholine, norepinephrine, substance P, and dopamine [124] and stimulate adenylate cyclase activity [125] in the central nervous system [124]. Many of the varying effects of opiates on CBF and vascular responses are accounted for by these indirect effects, the agent's concentration, and by the distribution of the different opiate receptors within the vasculature. For example, μ-, δ-, and κ-receptor agonists can produce vasodilation, while ϵ-receptor agonists vasoconstrict [126].

In general, most currently available, clinically relevant opioids have little effect on CBF, $CMRO_2$, and ischemic tolerance. Further, the nonspecific opiate receptor antagonist naloxone does not improve outcomes after focal ischemia in cats [127] or primates [128, 129]. More recently, several investigators have evaluated the potential therapeutic effect of κ-receptor

agonists. This follows, in large part, from the finding that brain levels of the κ-receptor agonist dynorphin are markedly reduced in regions previously exposed to ischemia [130]. Clinically, κ-receptor agonists (e.g., nalbuphine) appear to mediate analgesia and sedation. There is also mounting evidence that κ-receptor agonists may be of benefit [131–134] because they attenuate excitotoxic mechanisms presynaptically [135, 136] and decrease intracellular calcium entry [135, 137], not because of blood flow effects [138, 139]. These agents have efficacy even if administered 6 hours after the onset of focal ischemia [134, 140–142]. The κ_1 subtype appears to be the specific κ-receptor that is involved in the mechanism of brain injury [139, 143]. Further development and testing of these agents in both neuroprotection and pain management is likely.

■ Propofol

Propofol *(2,6-di-isopropyl phenol)* depresses cerebral metabolism by an unknown mechanism, decreases CBF in a manner linked to decreased $CMRO_2$ [144–146] and reduced cerebral electrical activity [147], and attenuates the increase in extracellular concentration of glycine that ordinarily accompanies ischemia [101]. The mechanism of reduced CBF is not likely to be vascular because in vitro propofol causes vasodilation, not vasoconstriction [148]. Relative to halothane/nitrous oxide anesthesia, propofol improves CBF recovery but not neuropathologic changes following experimental global ischemia [149]. In the setting of transient focal ischemia, propofol's potential neuroprotection has been compared to other anesthetics with conflicting results. Improved neurological outcome and decreased neuronal damage relative to fentanyl/nitrous oxide have been reported [150]. However, others have found no improvement in these parameters with propofol-treated rats as compared to halothane [151]. Although it has not been directly tested against any of the barbiturates, it is unlikely to offer any substantial benefit over these agents. Propofol has a shorter half-life than thiopental, but it produces a similar degree of cardiovascular depression [152] and is currently much more expensive.

■ α_2-Adrenoreceptor Agonists

α_2-Receptor agonists are becoming more commonly used agents in clinical medicine and are frequently used as baseline anesthetics (e.g., urethane) in animal models of ischemia. The α_2-agonist dexmedetomidine produces sedation [153], decreases CBF, and transiently decreases ICP [154] without changing $CMRO_2$ [155, 156]. Binding sites for α_2-agonists within brain are most highly concentrated in areas involved with the con-

trol of cardiovascular function [157]. Cerebral arteries are rich with postsynaptic α_2-adrenoceptors [158] that, when stimulated, cause vasoconstriction [159]. The effector mechanism for both vasoconstriction and sedation involves a G protein [160] that inhibits adenylate cyclase and decreases cAMP accumulation [161].

Although these agents appear to be cerebroprotectants, the mechanism of protection may not be related to their ability to act at the α_2-receptor. For example, immediate, postischemic administration of idazoxan, an α_2-receptor antagonist, ameliorates brain injury in rats exposed to transient forebrain ischemia [162, 163]. The proposed mechanism of protection is accentuated catecholamine release within brain [162, 164]. However, the α_2-adrenergic agonist dexmedetomidine also improves neurological outcome from transient incomplete and focal ischemia [5, 165, 166] and is hypothesized to act by attenuating ischemia-induced catecholamine release within brain [167]. Because it is unlikely that both increases and decreases in brain catecholamines are protective, some other mechanism must be involved. For example, both idazoxan and dexmedetomidine could act at the imidazole receptor [168]. A supportive finding is that idazoxan (an α_2-receptor antagonist and an agent with activity at the imidazole receptor) is neuroprotective, whereas SKF 86466, a highly selective α_2-receptor antagonist without imidazole receptor activity, is not protective [168].

■ Benzodiazepines

Benzodiazepines decrease cerebral metabolism and blood flow [169–171]. At least a portion of their effect in brain is linked to modulation of postsynaptic responses to GABA and receptor-linked chloride channels [34]. Associated with GABA-induced, increased chloride conductance is a generalized reduction in EEG and brain function [172]. After ischemia, GABAergic neurons are preserved in hippocampus but with a decreased number of postsynaptic $GABA_A$-benzodiazepine binding sites. This suggests that benzodiazepines, by increasing receptor affinity, could be useful in reducing ischemic neuronal death, at least in the hippocampus [173]. Also consistent with this hypothesis is the observation that enhanced GABA neurotransmission after cerebral ischemia reduces loss of hippocampal neurons [174, 175].

Benzodiazepines and barbiturates have been reported to have similar efficacy after incomplete global cerebral ischemia [176], but not following severe hypoxia. Seizure activity during reperfusion accentuates postischemic brain injury in cerebral cortex, thalamus, and brain stem [177], and diazepam has been shown to be particularly effective in ameliorating neocortical injury when there is a relatively high incidence of postischemic

seizures [177]. However, midazolam was not effective in ameliorating brain injury in a multiple cerebral embolic model [178].

■ Lidocaine

Lidocaine was originally evaluated as a neuroprotectant because, as a local anesthetic, it was hypothesized to partially preserve transmembrane ion gradients during ischemia. In addition, lidocaine could reduce release of excitatory amino acids during ischemia by blocking intracellular sodium influx. At high doses, lidocaine can reduce cerebral metabolism [179] but appears to have little direct effect on CBF [180].

Intravenous lidocaine can protect the brain from injury associated with cerebral air embolism [181, 182]. After transient focal ischemia, lidocaine as a bolus transiently improves brain electrical activity but does not reduce infarct size [183]. However, continuous intravenous infusion during both ischemia and reperfusion does result in decreased infarct volume and a higher regional cerebral blood flow [180]. The mechanism of protection is probably related to lidocaine's ability to inhibit ischemic depolarization, which occurs in the lesion periphery or penumbra. After global ischemia, lidocaine has provided variable levels of protection that were dependent on the drug dose, the accompanying baseline anesthetic of the study, and the duration of the ischemic insult [184–186].

■ Summary

A number of anesthetic agents have significant cerebroprotective potential and alter ischemic tolerance in vivo, at least within specific experimental conditions such as focal or incomplete, global cerebral ischemia. As compared to the unanesthetized state, each of these agents has some influence on CBF and metabolism, and many have significant effects on vascular responses to dilator stimuli. Relevant studies that provide clues to the mechanisms of anesthetic action in brain injury have been reviewed, and it is likely that these mechanisms are multifactorial and may overlap from one class of agents to another. Lastly, there is a clear need for further studies that specifically evaluate the neuroprotective mechanism of each agent, determine the effect on outcomes when the anesthetic is administered only as a posttreatment at clinically relevant concentrations, and compare anesthetics with the unanesthetized state when possible.

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