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 posts ischemic recovery period. More recent “bad news” suggests that this neuroprotective effect is not apparent after a long posts ischemic 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 cerebral 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.

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,
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. Béirne et al. [19] examined the effect of hal-