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REVIEW ARTICLE

Anesthetics, Cerebral Protection and Preconditioning

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Abstract

Background and objectives: Several studies demonstrate that cerebral preconditioning is a protective mechanism against a stressful situation. Preconditioning determinants are described, as well as the neuroprotection provided by anesthetic and non-anesthetics agents.

Content: Review based on the main articles addressing the pathophysiology of ischemia-reperfusion and neuronal injury and pharmacological and non-pharmacological factors (inflammation, glycemia, and temperature) related to the change in response to ischemia-reperfusion, in addition to neuroprotection induced by anesthetic use.

Conclusions: The brain has the ability to protect itself against ischemia when stimulated. The elucidation of this mechanism enables the application of preconditioning inducing substances (some anesthetics), other drugs, and non-pharmacological measures, such as hypothermia, aimed at inducing tolerance to ischemic lesions.

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Introduction

The ability to respond to stressful situations is a fundamental property of all living organisms [1]. Surviving a sublethal insult may result in a protective state to a subsequent lethal insult. This phenomenon is seen in various organs, particularly brain and heart, and called cerebral preconditioning (CP)

or ischemic tolerance (IT) [2]. The first in vivo evidences of CP dates back to the 1960s [3,4]. Nearly three decades have passed with no interest from researchers on this mechanism, until Kitagawa et al. [5] started the era of ischemic tolerance research.

The main pathophysiological aspects involved in cerebral ischemia/reperfusion are caused by the excitotoxic actions of glutamate, ATP consumption, changes in ionic homeostasis, and formation of free radicals. Anesthetics, hypothermia, sodium channel blockers, and ascorbic acid are among the many substances that provide protection to the nervous system acting on these points [6,7].

It occurs in two distinct time frames: early and late tolerance. Early tolerance main mechanism is the adaptation of membrane receptors, which can be achieved within minutes, but decreases rapidly within hours. Late tolerance, through gene activation with subsequent synthesis of new proteins, is achieved within hours and can last for several days [2].

In humans, transient ischemic attacks (TIAs) may be a clinical sign of preconditioning. Mimicking the mechanisms of this process of endogenous protection is therefore a potential strategy for stroke prevention [2].

The relevance of brain protection in clinical practice can be found during cardiopulmonary resuscitation [8] and before surgical procedures that intentionally require maintaining periods of cerebral ischemia/hypoperfusion. The anesthesiologist is then faced with the possibility of actively preparing the nervous system for the ischemia-reperfusion events and thereby preventing possible related injuries.

Pathophysiology of ischemia-reperfusion and neuronal injury

The brain performs its functions through complex signaling pathways between nerve cells. Information transmission between neurons depends on tissue integrity [9]. The central nervous system consumes high levels of oxygen and glucose, which are metabolized by oxidative phosphorylation. The normal cerebral blood flow in humans fluctuates around 50 $mL.100g^{-1}.min^{-1}$; when this value reaches about 10 $mL.100g^{-1}min^{-1}$, it is estimated that a potential neuronal loss occurs, which leads to neurological function deterioration.

Complete cerebral ischemia or decreased cerebral blood flow, followed by reperfusion, triggers deep changes in neuronal metabolism. During ischemia, there are: increased cell catabolism; decreased amount of ATP available; Na+/K+-ATPase dysfunction; intracellular sodium accumulation; changes in membrane potential; cellular edema; and increased activity of excitatory neurotransmitters, such as glutamate [10]. The anaerobic metabolism of glucose produces lactate and consequent increase in H+ concentration inside the cell [11].

With cerebral reperfusion, there is initially a supply of oxygen and glucose greater than the cell capacity to use it [12]. Hyperglycemia results in increased concentration of lactic acid, which follows the initial phase of ischemia and exacerbates post-ischemic injuries. Electrochemical reduction of oxygen molecules forms reactive oxygen species leading to oxidative stress [13,14]. Hydroxyl radical (OH^-), the most potent reactive oxygen species, acts on the breakdown of fatty acid molecules of the membrane. Catalase, superoxide dismutase, and glutathione peroxidase are enzyme systems involved in neutralizing these radicals. Ascorbic acid (vitamin C) and tocopherol (vitamin E) are also responsible for some protection against these radicals [15,16].

Gamma-Aminobutyric acid (GABA) and glycine are the nervous system main inhibitory neurotransmitters controlling the opening of chloride or potassium channels. GABA receptors are frequent targets of anesthetics that, besides reducing neuronal excitation, induce neuroprotection by reducing the excitotoxicity.

The major neuronal excitatory amino acid is glutamate, a metabotropic and ionotropic receptor agonist (NMDA and non-NMDA). Activation of ionotropic receptors results in the opening of an ion channel in the postsynaptic membrane. NMDA ionotropic glutamate receptors open calcium channels. Non-NMDA receptors open channels that are permeable to sodium and potassium. Metabotropic receptors are linked to G protein, a second messenger that has a guanidine nucleoside. The binding of glutamate to its metabotropic receptors results in the activation of phospholipases A_2 and C.

During reperfusion, synergistic action of reactive oxygen species and glutamate leads to increased metabolism of arachidonic acid into leukotrienes via lipoxygenase, thromboxanes, prostacyclins, and prostaglandins via the cyclooxygenase pathway [17-18]. These molecules increased concentration seems to be involved in cytotoxic edema and the damage of organelles and plasma membranes [19]. The action of glutamate results in increased concentration of intracellular calcium. Excess calcium ion has a harmful effect due to the activation of proteases and phospholipases.

Despite the great importance given to calcium regarding the pathophysiology of ischemia/reperfusion, several studies evaluating the effect of substances that decrease calcium entry into the cell failed to establish the efficacy of this approach in neuroprotection [10]. Voltage-independent calcium channels are divided into four subtypes, characterized by threshold activation, conductance, and location [20]. The N-type and L-type seem to be involved in the pathophysiology of ischemia/reperfusion. N-type channels are related to the release of neurotransmitters in the synaptic cleft and L-type channels are related to changes in neuron metabolism. Substances derived from dihydropyridine and phenylalkylamine act by blocking the L-type calcium channel. Experimental models of focal ischemia associate its use with a decrease in mortality and neurological function improvement [21].

Alpha-2 agonists in vivo have been shown to attenuate neurological injuries after ganglionic blockade with hexamethonium in rat models of incomplete cerebral ischemia [22]. The development of an anesthetic with an adjunct α-2 agonist action must include its use as a neuroprotective agent [23].

Nitric oxide (NO) is a gas that acts as a neuromodulator in glutaminergic synapses by oxidizing sulfhydryl residues of NMDA receptors, inactivating them [24]. NO can also react with oxygen radicals and generate reactive nitrogen species, which react with the proton (H+) and produce the potent hydroxyl radical [25].

Lipopolysaccharide (LPS) is a cell wall component of Gram-negative bacteria. A small dose of LPS can result in brain ischemic tolerance (BIT). This has been proven by a

number of experiments, which included both transient and permanent focal ischemia models. However, high doses of LPS had no effect on CP [26].

Consequences of cerebral ischemia/reperfusion may be limited to the action on membrane lipids of cellular proteins and thus be quickly reversed. When changes are of sufficient magnitude to impair RNA transcription or alter the DNA itself, there will be cellular death, which is an irreversible phenomenon [10].

In cerebral infarction, necrosis occurs in the central area. Peripheral changes are not as severe as central changes; neurons die more slowly and mainly by apoptosis [27]. This process involves the mitochondrial cytochrome-c, caspase activation, and other pro-apoptotic factors. Cytokines, such as IL-1, contribute to the occurrence of this neurodegeneration.

Therapies with potential to act on various neuroprotective inducers are more effective than mono-focal therapies. For example, MK-801 (NMDA antagonist) is an excitotoxicity suppressor of cell death, but seems to exacerbate apoptotic injury [24].

Determinants of ischemic tolerance

Several animal models experiments of global and focal ischemia confirmed that the ischemic tolerance concept, introduced two decades ago and initially based on myocardium observations, may be extended to cerebral ischemic injury [28-30]. Therefore, it is understood that brief ischemic episodes protect the brain against subsequent more severe ischemia.

Besides sublethal ischemia, other conditions, such as hyperthermia [31], hypothermia [32], hypoglycemia [33], and pharmacological agents (e.g., antibiotics, erythropoietin, acetylsalicylic acid, and volatile anesthetics) induce ischemic tolerance [34-37].

The initial phase of ischemic tolerance (up to 30 minutes after a sublethal insult) is likely due to metabolic transmembrane flow events. The delayed phase of tolerance (after 24 hours) involves genetic induction and protein synthesis [38,39]. Molecules, such as adenosine, hypoxia inducing factor-1α, TNF-α, reactive oxygen species, NO, and other events involving NMDA receptor activation and intracellular calcium influx have been implicated in tolerance to ischemia.

Although the precise mechanisms of IT are not fully elucidated, CP is a therapeutic strategy for brain damage improvement in patients at high risk for ischemic brain injury.

Inflammation

Cerebral ischemia leads to immune reaction, with nonspecific inflammatory cell infiltration, peripheral leukocytes migration to brain, and microglia activation [40]. Moreover, ischemic neurons release inflammatory cytokines (IL-1 and TNF-α). Glia lead to the generation of adhesion molecules (selectins, integrins, intercellular adhesion) in cerebral vasculature, resulting in increased permeability of the blood-brain barrier (BBB) and culminating in edema formation [41,42].

Cytokine secretion and proteases, such as metalloproteinases, causes further disruption of the extracellular matrix and BBB. Although IL-1 is responsible for cerebral ischemic injury, the functions of other cytokines such as IL-6 (a proinflammatory cytokine) and IL-10 (an anti-inflammatory cytokine) are less clear. TNF-α is not only responsible for ischemic brain inflammation [43], but plays a role in propagating brain injury [44,45].

Nimesulide, a cyclooxygenase-2 inhibitor, has been shown to attenuate lesion in the hippocampus CA1 region in a gerbil model when administered orally or intraperitoneally as a pre- or post-treatment of up to 24 hours [46]. Additional experimental studies in animal models are needed to confirm these findings and frame them in a clinical paradigm.

Immunosuppressants, such as cyclosporine and acrolimus, are immunophilin and calcineurin inhibitors and potent apoptosis inducers. Administration of both agents for three days before ischemia provided seven days of neuroprotection in an animal model of global cerebral ischemia [47]. These agents also attenuated the activity of calcineurin in CA1 and CA3 and dentate gyros of hippocampus within 24 hours after ischemic injury. Pretreatment with cyclosporin inhibits the dephosphorylation of proapoptotic BAD protein. Cyclosporin inability to cross the intact BBB is a significant therapeutic concern.

These agents require more rigorous testing for post-ischemia treatment in different animal species and global models of cerebral ischemia [39].

Glycemia

A series of traumatic brain injury studies of animal models [48], focal cerebral ischemia [49], and global cerebral ischemia [50] found that glycemic control is a critical factor in IT. Several mechanisms have been proposed for brain injury genesis, including marked release of excitatory amino acids (EAAs), reduced release of neuroinhibitory transmitters [51], massive deposition of neutrophils [52], and mitochondrial damage by cytochrome-c activation, caspase-3 and caspase-9 [53]. These studies led to clinical observations that a poor glycemic control increases brain damage in ischemic stroke [54,55]. Glycemic control with insulin showed better neurologic outcomes in critically ill patients, as well as in patients undergoing cardiac surgery [55,56]. Although insulin therapy has shown improvement in brain damage in animal models of global cerebral ischemia [57], further clinical trials of glycemic control management with insulin therapy are needed.

Temperature

Functional outcome and histopathology of animal model experimental studies of global and focal cerebral ischemia provided evidence for the importance of brain temperature [58]. During a cerebral ischemic event, hyperthermia leads to incomplete normalization of phosphate metabolism, which results in microvascular injury and edema, leading to increased mortality [58]. Spontaneous increases in body temperature have been reported after experimental focal and global ischemia and may be a consequence of brain damage [59].

Induced mild (34°C) to moderate (30°C) hypothermia reduces ischemic brain injury after experimental cardiac arrests [60]. Neuroprotective mechanisms induced by hypothermia may be multifactorial and include biosynthesis pre- and post-synaptic processes, release and absorption of EAAs, decreased production of hydroxyl radical, membrane lipoprotein protection, intracellular acidosis, and demand for oxygen by the injured brain [61].

The neuroprotection induced by hypothermia can be divided into acute and delayed. Experts agree that the activation of cell signaling molecules, such as adenosine receptors, tyrosine kinase, and potassium channels, is important for the development of CP-induced ischemic or anesthetic events. Studies show that adenosine receptor activation may lead to the opening of ATP-sensitive potassium channels, which induces the production of oxygen free radicals to activate the Ras/Raf pathway. This pathway is part of the kinase cascade and responsible for activating the Ras protein, a product of a proto-oncogene acting as a G protein (transmits signal through the exchange of GDP/GTP) and is associated with plasma membrane. The Ras protein activates a kinase cascade and is responsible for successive phosphorylations, starting with Raf activation, responsible for the activation of other proteins, up to the last one (MAP), which will activate transcription factors that will act on gene transcription, resulting in increased expression of genes responsible for insulin production and other growth factors involved in CP [62-66].

Hypothermia also inhibits the high-mobility group HMG-I(Y), an important nuclear transcription protein responsible for increased expression of NO synthetase, cyclooxygenase-2, and cytokines that, in turn, are responsible for the development of post-ischemia brain lesions. However, it is unclear whether preconditioning hypothermia-induced inhibition of protein expression HMG-I (Y) plays a role in the development of acute, delayed or of both neuroprotective phases [67].

Nishio et al. [32] suggest that protein synthesis is required for developing preconditioning induced by hypothermia in the late neuroprotection phase.

Recent clinical trials have demonstrated better neurological outcome and reduced mortality in patients undergoing mild or moderate therapeutic hypothermia [67]. Future studies should incorporate other pharmacological neuroprotective strategies combined with hypothermia, in order to achieve better results.

Calcium channel antagonists

Ca^{2+} is the final common pathway in excitotoxic neuronal injury.

Nimodipine, a Ca^{2+} channel blocker, has been studied in experimental models of global cerebral ischemia. Subcutaneous administration of nimodipine failed to show any neurological, histological, or functional improvement in rat models of global cerebral ischemia [68,69]. However, treatment with intravenous nimodipine in a rabbit model reduced EEG recovery time, attenuated the decrease of extracellular Ca^{2+} and decreased BBB disruption. In this study, blood pressure was maintained at 100 mm Hg after ischemic insult, which offset the hypotensive adverse effects of nimodipine.

A double-blind, prospective, randomized trial of nimodipine in patients who had ventricular fibrillation outside hospitals failed to show any improvement in survival rate for one year; however, it did show some benefit in patients with resuscitation delayed for more than 10 minutes [70].

NMDA Receptor antagonists

Pre- and post-treatment with dextrorphan (NMDA receptor antagonist) improved histological damage in the hippocampus and cortex of ischemic model in rats and attenuated the loss of calcium-dependent protein kinase activity, such as calmodulin [71].

Although dizocilpine (another NMDA receptor antagonist) has shown significant histological neuroprotection in animal models of global cerebral ischemia [72], its use in clinical courses of ischemic insults produced significant adverse events (delirium, psychosis, hallucinations) [73].

GABA agonists

The premise of using gamma-Aminobutyric acid (GABA) or its agonists as neuroprotectors is based on their inhibitory properties in opening chloride channels [39]. Pretreatment with GABA demontratedly attenuates histological injury and improves the nervous system's behavior in a model of global cerebral ischemia in gerbils [74]. The treatments after the insult failed to show any improvement in these parameters.

Clormetiazol, a GABA agonist with anticonvulsant, hypnotic, and sedative properties, showed no improvement in histological damage or neurobehavior in a murine model of global cerebral ischemia [75]. Furthermore, local infusion of clormetiazol through microdialysis did not change the release of dopamine, serotonin or its induced-ischemia metabolitesin the ischemic stratum [75].

Intraperitoneal administration of G-hydroxybutyrate improved histological and neurobehavioral injury in a murine model of global cerebral ischemia [76].

The use of tiagabine, a selective inhibitor of GABA uptake, resulted in no histological improvement in a gerbil model when given as a pretreatment [77].

Anticonvulsants

The basis for using anticonvulsants in ischemic neuroprotection is its ability to stabilize neurons by hyperpolarization of membrane potential by blocking voltage-dependent Na^+ channel [39].

Treatment with phenytoin reduces K^+ accumulation in cerebrospinal fluid of animals undergoing circulatory arrest. Some studies of phenytoin therapy showed decreased cerebral edema, increased activity of Na^+/K^+ ATPase enzyme, decreased intracellular Na^+ concentration, and reduced accumulation of lactate and free fatty acids [78].

The use of lamotrigine reduced the increase of extracellular glutamate levels induced by ischemia, with histologic improvement in models of global cerebral ischemia (rats and gerbils) [79].

Erythromycin

Studies of erythromycin showed improvement in neurological function and increased neuronal survival after ischemia [80].

The neuroprotective effect of erythromycin in mice is associated with increased expression of anti-apoptotic gene bcl-2.

Pretreatment with erythromycin 12 hours before the ischemic event improved postischemic neuronal survival in hippocampal areas (CA1 and CA3) and reduced functional deficit. Studies indicate that the neuroprotective effect of erythromycin lasts up to seven days.

This erythromycin effect suggests a clinical strategy of ischemic preconditioning, which could be beneficial to patients scheduled for surgical procedures associated with increased risk of perioperative cerebral ischemia (e.g., cardiovascular surgery or neurosurgery). Future studies are needed to determine the clinical role of this novel method of neuroprotection and clarify the molecular mechanisms involved.

Neuroprotection induced by anesthetics

Several studies *in vitro* [85] and *in vivo* in the last 20 years have reported neuroprotection induced by anesthesia [86,87] in different species [88-90] and in hemispheric [92] and global [93,95] models of focal ischemia [91,92].

Most anesthetic agents have neuroprotective properties, although neuroprotection is not correlated with anesthetic efficacy. The use of anesthetics to induce neuroprotection depends not only on its potency, but also on the administration method, side effects, and patient tolerability.

A major concern is the apparent lack of long-term neuroprotective effects of some anesthetic agents [81.82].

GABAergic agents

The main receptor of volatile anesthetics is believed to be GABA [83].

The inhibitory neurotransmission via GABA receptor modulation contributes to anesthesia. Therefore, it is not surprising that reduced neuronal excitability induced by GABAergic agents may also reduce excitotoxicity.

Sanders et al. [7] reported neuroprotection induced by GABAergic anesthetic agents using examples of volatile and intravenous agents. This study considered the suppression of cerebral metabolic rate (CMR) as a possible mechanism of neuroprotection induced by anesthetics.

Volatile anesthetics

The neuroprotective potential of volatile anesthetics, particularly isoflurane, was highlighted by some authors [84]. Isoflurane has shown to be an anesthetic agent with significant neuroprotective effects, with the ability to reduce excitotoxicity.

Isoflurane proved to be a superior neuroprotective agent to a combined regimen of nitrous oxide and fentanyl in mice assessed three days after bilateral carotid artery occlusion in cognitive and histological function tests [94]. Additionally, in a model of traumatic brain injury in rats, isoflurane provided better neuroprotection than fentanyl when both were administered in combination with nitrous oxide [28].

Some studies suggest that isoflurane reduces the cerebral metabolic rate and, therefore, inhibits excitotoxicity. This effect appears to be independent of peri-ischemic cerebral blood flow, despite isoflurane vasodilating properties [95]. The neuroprotective effect of anesthetics is also independent of intracranial pressure.

Isoflurane reduced neurological deficit in about 20% of the sample in a canine model of cardiac arrest, compared to control group [88]. Administration of isoflurane for 5 hours post-injury showed reduced excitotoxicity mediated by α-amino-*d*-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) injury, a subtype of glutamate receptors [86]. In contrast with pentobarbital, which was effective only at a cerebral suppression dose, isoflurane was effective in anesthetic doses.

Another volatile anesthetic, desflurane, also showed neuroprotective properties equivalent to those of isoflurane in an animal model of incomplete cerebral ischemia, and both agents proved to be superior to fentanyl and nitrous oxide based anesthesia [96].

In vitro studies showed that the effect of reducing cerebral metabolic rate is not sufficient to explain the neuroprotective effects of volatile anesthetics.

Sanders et al. [7] used gabazine, a GABA receptor antagonist, to elucidate whether this effect could be attributed to these receptors. Gabazine showed a similar neuroprotective mechanism. Likewise, Bickler et al. [97] showed that the neuroprotective effect of isoflurane is dependent on GABA receptors with the use of bicuculline, another GABA receptor antagonist.

Volatile anesthetics may also protect against glutamate excitotoxicity and promote its uptake. This action cannot be obtained with pentobarbital, an intravenous anesthetic agent that also exerts neuroprotective effect [98]. Interestingly, isoflurane and thiopental share the ability to prevent decrease in phosphorylation of focal adhesion kinase (FAK pp125), induced by oxygen-glucose deprivation in vitro. The pp125 FAK interacts with cell survival cascades mediated by MAPK (ERK1 and 2) and AKT. However, despite interaction with these pathways, isoflurane showed no anti-apoptotic properties [82].

Intravenous anesthetics

Barbiturates were introduced as effective neuroprotective agents and considered the "gold standard", compared to other neuroprotective agents. However, more recent data refute this status. In the early 1970s, Yatsu et al. [99] reported that metohexital had neuroprotective activity. This study was followed by a series of studies reporting the neuroprotective efficacy of this class of agents. However, initial studies showed no temperature control and this led to overestimation of these drugs' effects.

In more controlled settings, barbiturates provide some protection, but not in terms of an impressive suppression of cerebral metabolic rate.

There was no difference in infarct volume after transient focal cerebral ischemia when comparing the use of low and high doses of thiopental, although these doses have clear differences in the ability to produce EEG suppression and, therefore, in brain metabolism [100]. Pentobarbital showed 25% reduction of infarct volume in a model of middle cerebral artery occlusion in rats 25% [101].

Direct comparison between metohexital and isoflurane shows that isoflurane MAC 2 was more potent against severe ischemia in rats than metohexital (0.1 $mg.kg^{-1}.min^{-1}$). The depression effect of cerebral metabolic rate was similar

for both drugs; however, unlike isoflurane, metohexital anesthetic doses have no neuroprotective effects during complete ischemia [102].

Barbiturates have neuroprotective efficacy against less severe insults. Milde et al. [103] found no difference between thiopental and isoflurane during temporary focal ischemia. However, a previous study had shown that in baboons, thiopental was a neuroprotective agent superior to isoflurane, although this study has shown the major hemodynamic difference bias between groups [104].

Zausinger et al. [105] recently compared in a model of transient focal ischemia in rats two combination therapies: the common treatment regimen (CTR) with nimodipine, mannitol, dexamethasone, and methohexital and the alternate treatment regimen (ATR) with magnesium, tirilazad, and mild hypothermia. Monotherapy with metohexital was effective and dexamethasone, mannitol, and nimodipine, alone or in combination, were not effective. CTR was not more effective than metohexital as a therapy, although it significantly reduced infarct volume. ATR was very effective and reduced infarction in 73% of samples without resulting in neurological deficit. This effect was significantly higher than CTR. Furthermore, hypothermia has shown neuroprotective effects in clinical trials [106], and pharmacological agents are likely to be judged as adjuvant therapy in this setting. In this study, barbiturates showed no additional protective benefit over hypothermia alone [107].

Clinical trials investigating the neuroprotective effects of barbiturates yielded contradictory results. Ward et al. [108] used barbiturates in 53 patients with traumatic skull-brain injury, and neurological outcome was similar to the control group.

In contrast to hypothermia, thiopental is an ineffective neuroprotective agent to follow cardiac arrest [109]. Thiopental administered at doses to produce EEG suppression [110] was ineffective in preventing strokes in patients with coronary artery bypass grafting. Thiopental was also associated with prolonged extubation and higher pressure requirements. In contrast, Nussmeier et al. [111] showed that thiopental exerted neuroprotection during cardiac surgery with cardiopulmonary bypass at normothermia [111] and reduced stroke incidence. Numerous differences in study methodologies could explain this discrepancy, which included air embolism, normothermia, hypothermia, and duration of therapy with barbiturates. However, this study of 182 patients is the only clinical trial suggesting the neuroprotective effect of barbiturates.

Thus, barbiturates may provide modest neuroprotection, but are not superior to other anesthetics, besides being potentially less additives when combined with hypothermia.

Propofol

Propofol has proved itself to be neuroprotective *in vivo* in models of focal [112] and Global [113] cerebral ischemia. This anesthetic-induced neuroprotection is most likely due to its antioxidant effects, the activation of its phenolic hydroxyl group. However, the hypothesis of CP induced by its effect on glutamate uptake, dopamine release or GABA receptor activation is not dismissed. The use of propofol also resulted in up-regulation of Bcl-2 and mdm-2 expression and down-regulation of Bax expression after brain ischemia in rats, which show an anti-apoptotic action of this drug. However, this action has not been histologically documented [114].

Clinically, cerebral suppression doses of propofol were not superior to sufentanil after open-heart surgery, assessed by the incidence of cognitive dysfunction, depression, or anxiety [115].

Alfa-2 agonists

The use of *in vivo* α2-agonists agents reduced neurological blockade after ganglionic injury with hexamethonium in a model of incomplete cerebral ischemia in rats [116]. This neuroprotective effect is partially reversed by intravenous administration of norepinephrine and epinephrine.

Subsequently, it became evident that neurological outcome is improved in rats receiving clonidine after incomplete cerebral ischemia by decreasing high catecholamine levels in blood [117].

Administration of dexmedetomidine pre-ischemia significantly reduced the levels of plasma catecholamines and decreased neurological comorbidities at functional and pathophysiological parameters [118]. Furthermore, Maier et al. [119] reported neuroprotective effects even when dexmedetomidine was administered in a model of transient focal ischemia in rabbits (plasma concentration 4 $ng.mL^{-1}$) [119].

The clinical use of α2-agonists as neuroprotective agents has not been determined.

NMDA antagonists

Ketamine, nitrous oxide, and xenon have anesthetic action by antagonizing NMDA glutamate receptors. The key-role of NMDA receptor in neurotoxicity led to numerous investigations of these anesthetics' potential to induce neuronal survival after injury.

The use of this class of agents has been hampered by psychomimetic effects associated with neuronal vacuolation in the posterior cingulate and retrosplenial cortex [120]. These psychomimetic side effects may worsen during ischemia [121], adding concern regarding the use of these agents as neuroprotectors.

While in vitro ketamine shows neuroprotective effects [122], *in vivo* results were not consistent. Proescholdt et al. [123] reported that S-(+) ketamine showed neuroprotective potency over R-(+) ketamine and racemic mixture. This difference in neuroprotective efficacy is consistent with the larger hypnotic and analgesic effects of S-(+) ketamine.

Very high doses of ketamine are necessary to achieve its ischemic protection ability [124]. However, high doses increase the risk of adverse effects, such as seizures and psychomimetic disorders. Nevertheless, high-dose ketamine has neuroprotective effects on cortical ischemia *in vivo* [123-124].

Ketamine was similar to remifentanil in a randomized controlled trial comparing the neuroprotective efficacy in open-heart surgery in combination with propofol [125]. The vasodilatory effect of ketamine may increase emboli movement, an event that could reduce its neuroprotective effect.

Arrowsmith et al. [126] reported a neuroprotective effect of this anesthetic during cardiopulmonary bypass (CPB), with perioperative application of the NMDA antagonist remacemide, although it was only similar to a secondary endpoint.

One hundred and seventy-one patients were tested with a neuropsychological battery pre- and post-operatively. There was no significant difference between groups on individual tests; however, the overall change in the postoperative period was better in the remacemide group.

Nitrous Oxide

Nitrous oxide has the neuroprotective and neurotoxic characteristics of a NMDA antagonist [127]. However, numerous studies have identified that the neuroprotection induced by nitrous oxide combined with an opioid is less potent than that induced by an inhaled anesthetics. Recently, experiments demonstrated that nitrous oxide has no neuroprotective effects in rats [128].

Xenon

Xenon's ability to act as a neuroprotective agent was demonstrated in several neuronal injury paradigms.

Xenon *in vitro* reduced cortical injury in rats, induced by NMDA, glutamate, or oxygen deprivation [129]. Another *in vitro* study showed that 50% xenon might reduce neuronal cell death induced by hypoxia [130], an effect that could be partly antagonized by calcium.

In clinical practice, xenon administration is usually given in combination with other anesthetics. Recently, it was demonstrated that co-administration of isoflurane synergistically increases xenon neuroprotection in vitro. This can be of great clinical importance, as xenon on its own is not sufficiently potent to induce anesthesia because of its higher MAP value (63-71%), aside from being extremely expensive. Additionally, the possibility of synergic multimodal therapies administration is likely to provide long-term neuroprotection.

Xenon attenuated neuronal damage induced by N-methyl-D-aspartate (NMDA) administration in rats [129]. Sanders et al. [130] reported its neuroprotective effect in a model of focal ischemia with 70% xenon administration during ischemia induced by cerebral artery occlusion in rats and showed a significant reduction in total infarct size, cortical and subcortical, compared to nitrous oxide [130]. Xenon provided superior neurocognitive protection than nitrous oxide, as shown by two of the three cognitive tests performed 24 hours after ischemia.

In a study evaluating the effect of xenon on a model of cardiopulmonary bypass (CPB) [131], we observed an attenuation of cognitive dysfunction caused by CPB up to 12 days after injury, an effect that was greater than that observed with the prototypical NMDA antagonist, MK801.

Some neurological injuries, such as perinatal brain injury, may not be predicted and, therefore, a neuroprotective agent cannot be administered before its occurrence. Therefore, research on the effectiveness of an agent with post-injury administration is important for clinical application in these scenarios. In a model of transient global ischemia, which occluded the middle cerebral artery in adult rats during 90 minutes, 50% xenon administered over 3 hours, starting 15 minutes after the insult, significantly reduced the neuronal damage in the striatum cortex. However, this study showed that 70% xenon was ineffective [132]. Theoretically, post-ischemic treatment with xenon may be used in neurological conditions, such as stroke.

Xenon MAP is estimated at 63% to 71%; thus, the concentrations needed for neuroprotection are significantly sub-anesthetic. In contrast with other drugs requiring anesthetic or supra-anesthetic doses to act as neuroprotective agents, xenon can be effective in clinically acceptable concentrations, when anesthesia is not required or may be detrimental (e.g., patients with cardiovascular impairment).

Unlike other NMDA antagonist receptors, xenon does not induce damage to the posterior cingulate and retrosplenial cortex [133]. Nagata et al. [134] demonstrated that xenon might improve the neurotoxic effect of other NMDA antagonists.

Recent in vitro investigations have suggested that xenon acts not only on NMDA receptors, but also activates the two pore domain of potassium channel TREK-1. TREK-1 channels are activated by intracellular acidosis, reduce neuronal excitability, and contribute to neuroprotection [135].

Conclusion

The brain has the ability to protect itself against ischemia when stimulated by appropriate factors. The elucidation of this mechanism resulted in the possibility of applying CP-inducing substances, such as some anesthetics, in medical practice. In operations requiring periods of ischemia or cerebral hypoperfusion, the anesthesiologist may intervene with drug administration and non-pharmacological measures, such as hypothermia, aiming at inducing tolerance to ischemic lesions.

Thus, defining the best strategy for nervous system protection is of paramount importance in reducing intraoperative neuropsychological impairment.

Combined inhaled anesthetics, such as isoflurane and xenon, is a good pharmacological alternative for intraoperative CP consolidation and, perhaps, against nonsurgical damages. Future studies may elucidate the most effective drug combination that could contribute to a better management of IT.

References

1. Koerner IP, Alkayed NJ – Ischemic preconditioning. Em: Bhardwaj A, Alkayed NJ, Kirsch JR et al. – Acute stroke, bench to bedside. New York, Informa Helthcare, 2006;345-353.
2. Tatlisumak T, Durukan A – Preconditioning-induced ischemic tolerance: a window into endogenous gearing for cerebroprotection. Exp Transl Stroke Med, 2010;2:2.
3. Dahl NA, Balfour WM – Prolonged anoxic survival due to anoxia pre-exposure: Brain ATP, lactate, and pyruvate. Am J Physiol, 1964;207:452-456.
4. Wells BA, Keats AS, Cooley DA – Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. Surgery, 1963;54:216-223.
5. Kitagawa K, Matsumoto M, Tagaya M et al. – "Ischemic tolerance" phenomenon found in the brain. Brain Res, 1990;528:21-24.
6. Homi HM, Silva Junior BA, Velasco IT – Fisiopatologia da isquemia cerebral. Rev Bras Anestesiol, 2000;50:405-414.
7. Sanders RD, Ma D, Maze M – Anaesthesia induced neuroprotection. Best Pract Research Clin. Anaesthesiology, 2005;19:461-474.
8. Safar P – Cerebral resuscitation after cardiac arrest: research initiatives and future directions. Ann Emerg Med, 1993;22:324-349.
9. Lent R ¤ Os chips neurais: processamento de informações e transmissão de mensagens através das sinapses. Em: Lent R – Cem bilhões de neurônios?, 2ª Ed., São Paulo, Atheneu, 2010;111-145.

10. Farooqui AA, Haun SE, Horrocks LA – Ischemia and hypoxia. Em: Siegel GJ – Basic neurochemistry: molecular, cellular, and medical aspects, 5ª Ed., New York, Raven Press, 1994;867-883.
11. Plum F – Mediators and antagpnism in seconday brain damage. In vivo and in vitro control of acid-base regulation of brain cells during ischemic and selective acidic exposure. Acta Neurochir, 1993;57:57-63.
12. Dietrich WD – Morphological manifestation of reperfusion injury in brain. Ann N Y Acad Sci, 1994;723:15-24.
13. Lai JC – Oxidative metabolism in neuronal and non-neuronal mitochondria. Can J Physiol Pharmacol, 1992;70:130-137.
14. Abe K, Aoki M, Kawagoe J et al. – Ischemic delayed neuronal death. A mitochondrial hypothesis. Stroke, 1995;26:1478-1489.
15. Traystman RJ, Kirsch JR, Koehler RC – Oxygen radical mechanisms of brain injury following ischemia and reperfusion. J Appl Physiol, 1991;71:1185-1195.
16. Yue TL, Barone F, Gu JL et al. – Brain alfa-tocoferol levels are not altered following ischemia/reperfusion induced cerebral injury in rats and gerbils. Brain Res, 1993;610:53-56.
17. Ikeda Y, Long DM – The molecular basis of brain injury and brain edema: the role of oxygen free radicals. Neurosurgery, 1990;27:1-11.
18. Oh MS, Betz AL – Interaction between free radicals and excitatory amino acids in the formation of ischemic brain edema in rats. Stroke, 1991;22:915-921.
19. Wahl M, Schilling L, Unterberg A et al. – Mediators of vascular and parenchymal mechanisms in secondary brain damage. Acta Neurochir, 1993;57:64-72.
20. Peruche B, Krieglstein J – Mechanisms of drug actions against neuronal damage caused by ischemia – an overview. Prog Neuropsychopharmacol Biol Psychiatry, 1993;17:21-70.
21. Gustafson I, Edgren E, Hulting J – Brain-oriented intensive care after resuscitation from cardiac arrest. Resuscitation, 1992;24:245-261.
22. Werner C, Hoffman WE, Thomas C et al. Ganglionic blockade improves neurologic outcome from incomplete ischemia in rats: partial reversal by exogenous catecholamines. Anesthesiology, 1990;73:923–929.
23. Ma D, Hossain M, Rajakumaraswamy N et al. – Combination of xenon and isoflurane produces a synergistic protective effect against oxygen glucose deprivation injury in a neuronal-glial co-culture model. Anesthesiology, 2003;99:748–751.
24. Crow JP, Beckman JS – The role of peroxynitrite in nitric-oxide mediated toxicity. Curr Top Microbiol Immunol, 1995;196:57-73.
25. Nakashima MN, Yamashita K, Kataoka Y et al. – Time course of nitric oxide synthase activity in neuronal, glial, and endothelial cells of rat striatum following focal cerebral ischemia. Cell Mol Neurobiol, 1995;15:341-349.
26. Tatlisumak T, Durukan A – Preconditioning-induced ischemic tolerance: a window into endogenous gearing for cerebroprotection. Exp Transl Stroke Med, 2010;2:2.
27. Dirnagl U, Iadecola C, Moskowitz MA – Pathobiology of ischaemic stroke: an integrated view. Trends in Neuroscience, 1999;22: 391-397.
28. Liu Y, Kato H, Nakata N et al. – Protection of rat hippocampus againstis chemic neuronal damage by pretreatment with sublethal ischemia. Brain Res, 1992;586:121-124.
29. Nishio S, Taki W, Uemura Y et al. – Ischemic tolerance due to the induction of HSP70 in a rat ischemic recirculation model. Brain Res, 1993;615:281-288.
30. Murry CE, Jennings RB, Reimer KA – Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation, 1986;74:1136.
31. Chopp M, Chen H, Ho KL et al. – Transient hyperthermia protects against subsequent fore brain ischemic cell damage in the rat. Neurology, 1989;39:1396-1398.
32. Nishio S, Yunoki M, Chen ZF et al. – Ischemic tolerance in the rat neocortex following hypothermic preconditioning. J Neurosurg, 2000;93:845-851.
33. Bergstedt K, Hu BR, Wieloch T – Initiation of protein synthesis and heat shock protein 72 expression in the rat brain following severe insulin induced hypoglycemia. Acta Neuropathol, 1993;86:145-153.
34. Huber R, Kasischke K, Ludolph AC et al. – Increase of cellular hypoxic tolerance by erythromycin and other antibiotics. Neuroreport, 1999;10:1543-1546.
35. Riepe MW, Kasischke K, Raupach A – Acetylsalicylic acid increases tolerance against hypoxic and chemical hypoxia. Stroke, 1997;28:2006-2011.
36. Dawson TM – Preconditioning mediated neuroprotection through erythropoietin? Lancet, 2002;359:96-97.
37. Kapinya KJ, Lowl D, Futterer C et al. – Tolerance against ischemic neuronal injury can be induced by volatile anesthetics and isinducible NO synthase dependent. Stroke, 2002;33:1889-1898.
38. Barone FC, White RF, Spera PA et al. – Ischemic preconditioning and brain tolerance: temporal histological and functional outcomes, protein synthesis requirement, and interleukin-1 receptor antagonist and early gene expression. Stroke, 1998;29:1937-1950.
39. Weigl M, Tenze G, Steinlechner B et al. – A systematic review of currently available pharmacological neuroprotective agents as a sole intervention before anticipated or induced cardiac arrest. Resuscitation, 2005;65:21-39.
40. Zheng Z, Lee JE, Yenari MA – Stroke: molecular mechanisms and potential targets for treatment. Curr Mol Med, 2003;3:361-372.
41. Han HS, Yenari MA – Cellular targets of brain inflammation in stroke. Curr Opin Investig Drugs, 2003;4:522-529.
42. Danton GH, Dietrich WD – Inflammatory mechanisms after ischemia and stroke. J Neuro pathol Exp Neurol, 2003;62:127-136.
43. Ginis I, Jaiswal R, Klimanis D et al. – TNF-alpha-induced tolerance to ischemic injury involves differential control of NF-kappa B transactivation: the role of NF-kappa B association with p300 adaptor. J Cereb Blood Flow Metab, 2002;22:142-152.
44. Gary DS, Bruce-Keller AJ, Kindy MS et al. – Ischemic and excitotoxic brain injury is enhanced in mice lacking the p55 tumor necrosis factor receptor. J Cereb Blood Flow Metab, 1998;18:1283-1287.
45. Bruce AJ, Boling W, Kindy MS et al. – Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. Nat Med, 1996;2:788-794.
46. Candelario-Jalil E, Alvarez D, Gonzalez-Falcon A et al. – Neuroprotective efficacy of nime sulide against hippocampal neuronal damage following transient forebrain ischemia. Eur J Phahrmacol, 2002;453:189-195.
47. Uchino H, Minamikawa-Tachino R, Kristian T et al. – Differential neuroprotection by cyclosporine A and FK506 following ischemia corresponds with differing abilities to inhibit calcineurin and the mitochondrial permeability transition. Neurobiol Dis, 2002;10:219-233.
48. Kinoshita K, Kraydieh S, Alonso O et al. – Effect of post traumatic hyperglycemia on contusion volume and neutrophilac cumulation after moderate fluid-percussion brain injury in rats. J Neurotrauma, 2002;19:681-692.
49. Chew W, Kucharczyk J, Moseley M et al. – Hyperglycemia augments ischemic brain injury: in vivo MR imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. AJNR Am J Neuroradiol, 1991;12:603-609.
50. Conroy BP, Grafe MR, Jenkins LW et al. – Histopathologic consequences of hyperglycemic cerebral ischemia during hypothermic cardiopulmonary by pass in pigs. Ann Thorac Surg, 2001;71:1325-1334.
51. Guyot LL, Diaz FG, O'Regan MH et al. – The effect of streptozotocin induced diabetes on the release of excitotoxic and other aminoacids from the ischemic rat cerebral cortex. Neurosurgery, 2001;48:385-390.

52. Lin B, Ginsberg MD, Busto R et al. – Hyperglycemia triggers massive neutrophil deposition in brain following transient ischemia in rats. Neurosci Lett, 2000;278:1-4.
53. Ding C, He Q, Li PA – Activation of cell death pathway after a brief period of global ischemia in diabetic and non diabetic animals. Exp Neurol, 2004;188:421-429.
54. Baird TA, Parsons MW, Phanh T et al. – Persistent post stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke, 2003;34:2208-2214.
55. Nuttall GA, Abel MD, Mullany CJ et al. – Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc, 2005;80:862-866.
56. VandenBerghe G, Schoonheydt K, Becx P et al. – Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology, 2005;64:1348-1353.
57. Auer RN – Non pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia. Ann NY Acad Sci, 2001;939:271-282.
58. Busto R, Dietrich WD, Globus MY et al. – Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab, 1987;7:729-738.
59. Zhao O, Memezawa H, Smith ML et al. – Hyperthermia complicates middle cerebral artery occlusion induced by an intraluminal filament. Brain Res, 1994;649:253-259.
60. Minamisawa H, Smith ML, Siesjo BK – The effect of mild hyperthermia and hypothermia on brain damage following 5, 10 and 15min of fore brain ischemia. Ann Neurol, 1990;28:26-33.
61. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med, 2002;346:549-556.
62. Koehler RC, Eleff SM, Traystman RJ – Global neuronal ischemia and reperfusion. Em: Paradis NA, Halperin HR, Nowak RM – Cardiac arrest: the science and practice of resuscitation medicine. Baltimore, Williams and Wilkins;1996:113-145.
63. Thompson CB – Apoptosis in the pathogenesis and treatment of disease. Science, 1995;267:1456-1462.
64. Dirnag LU, Iadecola C, Moskowitz MA – Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci, 1999;22:391-397.
65. Dawson TM, Dawson VL, Snyder SH – A novel neuronal messenger in brain: the free radical, nitricoxide. Ann Neurol, 1992;32:297-311.
66. Dawson TM, Dawson VL – Nitricoxide: actions and pathological roles. Neuroscientist, 1995;1:7-18.
67. Yuan HB, Huang Y, Zheng S et al. – Hypothermic preconditioning increases survival of purkinje neurons in rat cerebellar slices after an in vitro simulated ischemia. Anesthesiology, 2004;100:331-337.
68. Calle PA, Paridaens K, DeRidder LI et al. – Failure of nimodipine to prevent brain damage in a global brain ischemia model in the rat. Resuscitation, 1993;25:59-71.
69. Lazarewicz JW, Pluta R, Puka M et al. – Diverse mechanisms of neuronal protection by nimodipine in experimental rabbit brain ischemia. Stroke, 1990;21:108-110.
70. Roine RO, Kaste M, Kinnunen A et al. – Nimodipine after resuscitation from out- of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial. JAMA, 1990;264:3171-3177.
71. Arnowski J, Waxham MN, Grotta JC – Neuronal protection and preservation of calcium/calmodulin dependent protein kinase II and proteinkinase C activity by dextrorphan treatment in global ischemia. J Cereb Blood Flow Metab, 1993;13:550-557.
72. Li MM, Payne RS, Reid KH et al. – Correlates of delayed neuronal damage and neuro protection in a rat model of cardiac arrest induced cerebral ischemia. Brain Res, 1999;826:44-52.
73. Dietrich WD, Lin B, Globus MY et al. – Effect of delayed M K-801 (dizocilpine) treatment with or without immediate post ischemic hypothermia on chronic neuronal survival after global fore brain ischemia in rats. J Cereb Blood Flow Metab, 1995;15:960-968.
74. Shuaib A, Murabit MA, Kanthan R et al. – The neuroprotective effects of gamma-vinyl GABA in transient global ischemia: a morphological study with early and delayed evaluations. Neurosci Lett, 1996;204:1-4.
75. Thaminy S, Reymann JM, Heresbach N et al. – Is chlormethiazole neuroprotective in experimental global cerebral ischemia? A microdialysis and behavioral study. Pharmacol Bio chem Behav, 1997;56:737-745.
76. Vergoni AV, Ottani A, Botticelli AR et al. – Neuroprotective effect of gamma hydroxybutyrate in transient global cerebral ischemia in the rat. Eur J Pharmacol, 2000;397:75-84.
77. Iqbal S, Baziany A, Gordon S et al. – Neuroprotective effect of tiagabine in transient fore brain global ischemia: an in vivo microdialysis, behavioral, and histological study. Brain Res, 2002;946:162-170.
78. Artru AA, Michenfelder JD – A noxic cerebral potassium accumulation reduced by phenytoin: mechanism of cerebral protection? Anesth Analg, 1981;60:41-45.
79. Imaizumi S, Kurosawa K, Kinouchi H et al. – Effect of phenytoin on cortical Na(þ)-K(þ)-ATPase activity in global ischemic rat brain. J Neurotrauma, 1995;12:231-234.
80. Brambrink AM, Koerner IP, Diehl K et al. – The antibiotic erythromycin induces tolerance against transient global cerebral ischemia in rats (pharmacologic preconditioning). Anesthesiology, 2006;104:1208-1211.
81. Kawaguchi M, Kimbro JR, Drummond JC et al. – Isoflurane delays but does not prevent cerebral infarction in rats subjected to focal ischemia. Anesthesiology, 2000;92:1335-1342.
82. Kawaguchi M, Drummond JC, Cole DJ et al. – Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. Anesth Analg, 2004;98:798-805.
83. Franks NP, Lieb WR – Molecular and cellular mechanisms of general anaesthesia. Nature, 1994;367:607-614.
84. Harukuni I, Bhardwaj A – Mechanisms of brain injury after global cerebral ischemia. Neurol Clin, 2006;24:1-21.
85. Kudo M, Aono M, Lee Y et al. – Effects of volatile anesthetics on N-methyl-D-aspartate excitotoxicity in primary rat neuronal glial cultures. Anesthesiology, 2001;95:756-765.
86. Kimbro JR, Kelly PJ, Drummond JC et al. – Isoflurane and pentobarbital reduce AMPA toxicity in vivo in the rat cerebral cortex. Anesthesiology, 2000;92:806-812.
87. Harada H, Kelly PJ, Cole DJ et al. – Isoflurane reduces N-methyl-D-aspartate toxicity in vivo in the rat cerebral cortex. Anesth Analg, 1999;89:1442-1447.
88. Blanck TJ, Haile M, Xu F et al. – Isoflurane pretreatment ameliorates post ischemic neurologic dysfunction and preserves hippocampal Ca2C/calmodulin dependent proteinkinase in a canine cardiac arrest model. Anesthesiology, 2000;93:1285-1293.
89. MiuraY, Grocott HP, Bart RD et al. – Differential effects of anesthetic agents on outcome from near complete but not incomplete global ischemia in the rat. Anesthesiology, 1998;89:391-400.
90. Engelhard K, Werner C, Reeker W et al. – Desflurane an disoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. Brit J Anaesth, 1999;83:415-421.
91. Patel PM, Drummond JC, Cole DJ et al. – Isoflurane and pentobarbital reduce the frequency of transient ischemic depolarizations during focal ischemia in rats. Anesth Analg, 1998;86:773-780.
92. Soonthon-Brant V, Patel PM, Drummond JC et al. – Fentanyl does not increase brain injury after focal cerebral ischemia in rats. Anesth Analg, 1999;88:49-55.
93. Baughman VL, Hoffman WE, Miletich DJ et al. – Neurologic outcome in rat following in complete cerebral ischemia during halothane, isoflurane, or N2O. Anesthesiology, 1988;69:192-198.
94. Homi HM, Mixco JM, Sheng H et al. – Severe hypotension is not essential for isoflurane neuroprotection against fore brain ischemia in mice. Anesthesiology, 2003;99:1145-1151.

95. Mackensen GB, Nellgard B, Kudo M et al. – Periischemic cerebral blood flow (CBF) does not explain beneficial effects of isoflurane on outcome from near complete fore brain ischemia in rats. Anesthesiology, 2000;93:1102-1106.
96. Engelhard K, Werner C, Reeker W et al. – Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. Brit J Anaesth, 1999;83:415-421.
97. Bickler PE, Warner DS, Stratmann G et al. – Gamma-Aminobutyric acid-A receptors contribute to isoflurane neuroprotection in organotypic hippocampal cultures. Anesth Analg, 2003;97:564-571.
98. Miyazaki H, Nakamura Y, Arai T et al. – Increase of glutamate uptake in astrocytes: a possible mechanism of action of volatile anesthetics. Anesthesiology, 1997;86:1359-1366.
99. Yatsu FM, Diamond I, Graziano C et al. – Experimental brain ischemia: protection from irreversible damage with a rapid acting barbiturate (methohexital). Stroke 1972;3:726-732.
100. Schmid-Elsaesser R, Schroder M, Zausinger S et al. – EEG burst suppression is not necessary for maximum barbiturate protection in transient focal cerebral ischemia in the rat. Journal of Neurological Science, 1999;162:14-19.
101. Warner DS, Takaoka S, Wu B et al. – Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. Anesthesiology, 1996;84:1475-1484.
102. Baughman VL, Hoffman WE, Thomas C et al. – Comparison of methohexital and isoflurane on neurologic outcome and histopathology following incomplete ischemia in rats. Anesthesiology, 1990;72:85-94.
103. Milde LN, Milde JH, Lanier WL et al. – Comparison of thee ffects of isoflurane and thiopental on neurologic outcome and neuropathology after temporary focal cerebral ischemia in primates. Anesthesiology, 1988;69:905-913.
104. Nehls DG, Todd MM, Spetzler RF et al. – A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. Anesthesiology, 1987;66:453-464.
105. Zausinger S, Westermaier T, Plesnila N et al. – Neuroprotection in transient focal cerebral ischemia by combination drug therapy and mild hypothermia: comparison with customary therapeutic regimen. Stroke, 2003;34:1526-1532.
106. Whitelaw A, Thoresen M – Clinical trials of treatments after perinatal asphyxia. Curr Opin Ped, 2002;14:664-668.
107. Westermaier T, Zausinger S, Baethmann A et al. – No additional neuroprotection provided by barbiturate-induced burst suppression under mild hypothermic conditions in rats subjected to reversible focal ischemia. Journal of Neurosurgery, 2000;93:835-844.
108. Ward JD, Becker DP, Miller JD et al. – Failure of prophylac ic barbiturate coma in the treatment of severe head injury. Journal of Neurosurgery, 1985;62:383-388.
109. Brain Resuscitation Clinical TrialI Study Group – Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. New England Journal of Medicine, 1986;314:397-403.
110. Zaidan JR, Klochany A, Martin WM et al. – Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology, 1991;74:406-411.
111. Nussmeier NA, Arlund C, Slogoff S – Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology, 1986;64:165-170.
112. Kochs E, Hoffman WE, Werner C et al. – The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage followingin complete ischemia in rats. Anesthesiology, 1992;76:245-252.
113. Yamaguchi S, Midorikawa Y, Okuda Y et al. – Propofol prevents delayed neuronal death following transient fore brain ischemia in gerbils. Canadian Journal of Anaesthesia, 1999;46:593-598.
114. Engelhard K, Werner C, Eberspacher E et al. – Influence of propofol on neuronal damage and apoptotic factor safter incomplete cerebral ischemia and reperfusion in rats: a long-term observation. Anesthesiology, 2004;101:912-917.
115. Roach GW, Newman MF, Murkin JM – Multicenter study of perioperative ischemia. Anesthesiology, 1999;90:1255-1264.
116. Werner C, Hoffman WE, Thomas C et al. – Ganglionic blockade improves neurologic outcome from incomplete ischemia in rats: partial reversal by exogenous catecholamines. Anesthesiology, 1990;73:923-929.
117. Hoffman WE, Cheng MA, Thomas C et al. – Clonidine decreases plasma catecholamines and improves outcome from incomplete ischemia in the rat. Anesth Analg, 1991;73:460-464.
118. Hoffman WE, Kochs E, Werner C, et al. – Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat; Reversal by the a2-adrenergic antagonist atipamezole. Anesthesiology, 1991;75:328-332.
119. Maier C, Steinberg GK, Sun GH et al. – Neuroprotection by the a2-adrenoceptor agonist dexmedetomidine in a focal model of cerebral ischemia. Anesthesiology, 1993;79:306-312.
120. Olney JW, Labruyere J, Price MT – Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science, 1989;244:1360-1362.
121. Loscher W, Wlaz P, Szabo L – Focal ischemia enhances the adverse effect potential of N-methyl-D- aspartate receptor antagonists in rats. Neuroscience Letters,1998;240:33-36.
122. Choi DW, Koh JY, Peters S – Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. Journal of Neuroscience, 1988;8:185-196.
123. Proescholdt M, Heimann A, Kempski O – Neuroprotection of S(+) ketamine isomer in global fore brain ischemia. Brain Research, 2001;904:245-251.
124. Lees GJ – Influence of ketamine on the neuronal death caused by NMDA intherat hippocampus. Neuropharmacology, 1995;34:411-417.
125. Nagels W, Demeyere R, Van Hemelrijck J et al. – Evaluation of the neuroprotective effects of S (+) ketamine during open-heart surgery. Anesth Analg, 2004;98:1595-1603.
126. Arrowsmith JE, Harrison MJ, Newman SP et al. – Neuroprotection of the brain during cardiopulmonary bypass: a randomized trial of remacemide during coronary artery bypass in171 patients. Stroke, 1998;29:2357-2362.
127. Todorovic VJ, Todorovic SM, Mennerick S et al. – Nitrousoxide (laughinggas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nature Medicine, 1998;4:460-463.
128. Yokoo N, Sheng H, Mixco J et al. – Intraischemic nitrous oxide alters neither neurologic nor histologic outcome: a comparison with dizocilpine. Anesth Analg 2004;99:896-903.
129. Wilhelm S, Ma D, Maze M et al. – Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology, 2002;96:1485-1491.
130. Homi HM, Yokoo N, Ma D et al. – The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology, 2003;99:876-881.
131. Ma D, Yang H, Lynch J et al. – Xenon attenuates cardiopulmonary bypass induced neurologic and neurocognitive dysfunction in the rat. Anesthesiology, 2003;98:690-698.
132. David HN, Leveille F, Chazalviel L et al. – Reduction of ischemic brain damage by nitrous oxide and xenon. Journal of Cerebral Blood Flow and Metabolism, 2003;23:1168-1173.
133. Ma D, Wilhelm S, Maze M et al. – Neuroprotective and neurotoxic properties of the “inert” gas, xenon. Brith J Anaesth, 2002;89:739-746.
134. Nagata A, Nakao SS, Nishizawa N et al. – Xenon inhibits but N(2)O enhances ketamine-induced c-Fos expression in the rat posterior cingulated and retrosplenial cortices. Anesth Analg, 2001;92:362-368.
135. Gruss M, Bushell TJ, Bright DP et al. – Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Molecular Pharmacology, 2004;65:443-452.