CNS Drug Reviews
Vol. 13, No. 3, pp. 333–351
© 2007 The Authors
Journal compilation © 2007 Blackwell Publishing Inc.

Neuroprotective Effects of Propofol in Acute Cerebral Injury

Chiara Adembri[1], Luna Venturi[1],
and Domenico E. Pellegrini-Giampietro[2]

[1]Section of Anesthesiology and Intensive Care, Department of Critical Care and
[2]Department of Preclinical and Clinical Pharmacology, University of Florence, Italy

Keywords: Cerebral ischemia — Neurodegeneration — Neuroprotection — Neuroresuscitation — Propofol — Traumatic brain injury.

ABSTRACT

Propofol (2,6-diisopropylphenol) is one of the most popular agents used for induction of anesthesia and long-term sedation, owing to its favorable pharmacokinetic profile, which ensures a rapid recovery even after prolonged administration. A neuroprotective effect, beyond that related to the decrease in cerebral metabolic rate for oxygen, has been shown to be present in many *in vitro* and *in vivo* established experimental models of mild/moderate acute cerebral ischemia. Experimental studies on traumatic brain injury are limited and less encouraging. Despite the experimental results and the positive effects on cerebral physiology (propofol reduces cerebral blood flow but maintains coupling with cerebral metabolic rate for oxygen and decreases intracranial pressure, allowing optimal intraoperative conditions during neurosurgical operations), no clinical study has yet indicated that propofol may be superior to other anesthetics in improving the neurological outcome following acute cerebral injury. Therefore, propofol cannot be indicated as an established clinical neuroprotectant per se, but it might play an important role in the so-called multimodal neuroprotection, a global strategy for the treatment of acute injury of the brain that includes preservation of cerebral perfusion, temperature control, prevention of infections, and tight glycemic control.

Address correspondence and reprint requests to: Chiara Adembri, MD, PhD, Section of Anesthesiology and Intensive Care, Department of Critical Care, University of Florence, Viale Morgagni, 35, 50134 Firenze, Italy. Tel.: +39-055-4271219; Fax: +39-055-439303; E-mail: chiara.adembri@unifi.it

The authors have no conflict of interest.

INTRODUCTION

The failure in translating the successful results of drugs that attenuate acute neuronal injury from the experimental to the clinical setting has contributed to the great interest for the neuroprotective effects of molecules—such as minocycline derivatives, recombinant human erythropoietin (rh-Epo), and anesthetics—that are already used in the clinical practice with other indications. Indeed, many inhalatory and intravenous anesthetics share some properties, such as the reduction in the cerebral metabolic rate for oxygen ($CMRO_2$), the inhibition of glutamate release, and the positive modulation of $GABA_A$ receptor function, which are known to mitigate the detrimental effects of acute brain injury and thus are typical of the ideal neuroprotective drug (Kawaguchi et al. 2005; Koerner and Brambrink 2006).

In fact, the concept of pharmacologic brain protection originated in the operating room, when it was observed that general anesthesia increases the tolerance to hypoxia and to the disruption of metabolic substrate delivery (Wells et al. 1963; Michenfelder and Theye 1973; Warner 2004). It became clearer, later, that acute neuronal injury is a dynamic process in which neurons continue to die for a long time after an ischemic or traumatic insult (Patel 2004). This provides a useful window of opportunity for the pharmacologic treatment of acute brain injury, but brings up the question of whether anesthetic neuroprotection, often evident early after the insult, is maintained over a much longer recovery period. In many instances, the protective effects of anesthetics have been shown to be transient, thus questioning their utility as therapeutic agents for acute brain damage (Patel 2004; Warner 2004). A distinction, however, must be made between "neuroresuscitation," that is protection against acute ischemic or traumatic events that have already occurred, and "neuroprotection," that is strategies aimed at preventing potential brain damage under particular circumstances, such as neurosurgery and cardiac surgery, that may result in acute brain injury. In the latter case, anesthetics can certainly play an important role in decreasing the likelihood of brain damage and in gaining time for other neuroprotective approaches (multimodal neuroprotection) (Koerner and Brambrink 2006).

In this review, we will discuss the experimental and clinical data that have assessed the neuroresuscitative/neuroprotective effects of the intravenous anesthetic propofol in acute cerebral injury.

CHEMICAL PROPERTIES

Propofol (2,6-diisopropylphenol) is a short-acting intravenous agent that is chemically unrelated to other clinically used general anesthetics (James and Glen 1980). Propofol has a structural analogy with the antioxidant vitamin E, a fact that can partly explain its antioxidant properties. As shown in Figure 1, the presence of two isopropylic groups in ortho position with respect to the –OH group exerts a steric hindrance that prevents the approach

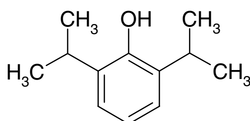

FIG. 1. Chemical structure of propofol (2,6-diisopropylphenol).

of hydrophilic molecules to the –OH itself. Hence, the molecule is highly hydrophobic and, as such, it was originally dissolved in Cremophor EL, a nonionic solubilizer and emulsifier whose main component is glycerol-polyethylene glycol ricinoleate. This solvent, however, turned out to be toxic, causing severe anaphylactic reactions (Briggs et al. 1982), and, therefore, propofol nowadays is presented in a 1% or 2% formulation consisting of an oil-and-water emulsion containing 10% soya bean oil, 1–2% egg phosphatide, and 2–5% glycerol. Although propofol emulsions are widely and successfully used, negative aspects still exist, such as emulsion instability, injection pain, need for antimicrobial agents to prevent sepsis, and a concern for hyperlipidemia-related side effects (Baker and Naguib 2005).

PHARMACOKINETIC PROPERTIES AND CLINICAL USE

The first report on the clinical use of propofol dates back to 1977 as an anesthesia-induction agent (Kay and Rolly 1977). Subsequently, propofol has been extensively employed also for short-term sedation, for example, during invasive procedures, as well as for long-term sedation in intensive care unit patients. The antiemetic and sedative-amnesic properties of propofol, together with its ability to relieve pruritus caused by intrathecal opioids (Borgeat et al. 1992) and by cholestasis (Borgeat et al. 1994) have greatly contributed to its clinical success (Liu and Gropper 2003).

Propofol exerts its sedative, hypnotic, and amnesic effects by interacting with an allosteric site on the $GABA_A$ receptor, potentiating currents elicited by low concentrations of GABA, increasing agonist efficacy, and, at higher concentrations, directly opening the $GABA_A$ receptor Cl^- channel in the absence of GABA (Concas et al. 1991; Orser et al. 1994). It also inhibits excitatory glutamate release by a presynaptic mechanism (Ratnakumari and Hemmings Jr. 1997). Interestingly, some of propofol's effects, such as antiemesis, postrecovery mood alterations, and postoperative dreaming (Mortero et al. 2001), might rely on inhibition of the cannabinoid degrading enzyme, with consequent increases in anandamide (AEA) and 2-arachidonylglycerol in the brain (Patel et al. 2003).

A three-compartment model best describes the pharmacokinetic profile of propofol, which is characterized by rapid distribution from blood to tissues, an equally rapid clearance of the molecule from the blood, and a slow return of the drug from the deep compartments (Kanto and Gepts 1989). These characteristics are responsible for the rapid onset, clear emergence, and lack of cumulative effects observed in clinical use. Propofol is mainly and rapidly metabolized in the liver to inactive metabolites (the glucuronide and the corresponding quinol glucuronides and sulfates). Other minor metabolites are detected in the urine. The total body clearance of propofol is greater than liver blood flow; therefore, an extrahepatic metabolism occurs. Hepatic and renal dysfunction do not significantly alter the pharmacokinetics of propofol (Fulton and Sorkin 1995).

Adverse properties of propofol include pain on injection (greatly relieved by adding long-chain triglycerides to the emulsion), apnea in up to 40% patients after induction, hypotension, and bradycardia (especially when used with other vagotonic drugs and in hypovolemic patients). Decreases in blood pressure induced by propofol are generally dose- and infusion-rate-dependent, and the effect is related to its vagotonic activity and to decreases in peripheral vascular resistance (Bryson et al. 1995). Other limitations and adverse effects

of propofol include the risk of extraneous microbial contamination of the emulsion formulation and lipidemia induced by repeated administration of the agent over time (infusions for periods exceeding 3 days produce progressive increases in levels of serum lipids, particularly triglycerides). The so-called propofol infusion syndrome, characterized by metabolic acidosis and/or rhabdomyolysis associated with progressive myocardial failure, although rare, has been increasingly reported over the years (Wysowski and Pollock 2006). The syndrome appears to be duration- and dose-related (usually, doses $\geq$5 mg/kg/h for >48 h) and more frequent in the pediatric population than in adults. Hence, presently propofol is not indicated for long-lasting sedation in children.

NEUROPROTECTION WITH PROPOFOL IN EXPERIMENTAL MODELS OF CEREBRAL ISCHEMIA

The neuroprotective effects of propofol have been investigated in numerous *in vivo* and *in vitro* models of cerebral ischemia (Table 1). Propofol has proved to be an efficacious neuroprotective agent, but the results have not always been entirely consistent, mostly depending on the variety of models, the different endpoints, and the modality of propofol administration selected by various laboratories. The administered dose of propofol also varied among different laboratories, depending on the severity of the model. A dose targeted at suppressing EEG bursts was reached by some but not all authors (see Table 1 for details).

In Vivo Experimental Models of Cerebral Ischemia

Propofol was postulated to be a possible beneficial agent against cerebral ischemia based on the assumption that it decreases cerebral blood flow (CBF) (with a parallel reduction in $CMRO_2$ and EEG activity) and mitigates intracranial pressure (ICP), all effects that are similar to those observed for barbiturates and other intravenous neuroprotective anesthetic agents (Kawaguchi et al. 2005; Koerner and Brambrink 2006). Initial studies, however, were performed using quite unconventional *in vivo* models of cerebral ischemia or inappropriate controls. Hence, propofol at first yielded contradictory results, in that it ameliorated the neurological outcome and neuronal damage following incomplete forebrain ischemia produced in rats by right common carotid artery occlusion combined with 30-min hemorrhagic hypotension (Kochs et al. 1992), but it was unable to improve the neurohistopathological outcome in rats undergoing permanent middle cerebral artery occlusion (MCAO) plus 60-min occlusion of both common carotid arteries (Tsai et al. 1994). Similarly, propofol failed to afford neuroprotection in cats exposed to a hypotension model that induced incomplete global ischemia (Weir et al. 1989) or in spontaneously hypertensive rats subjected to transient MCAO (Ridenour et al. 1992). However, a problem with these two latter studies is the use of halothane, which per se improves outcome from experimental ischemia, as a control treatment.

More consistent neuroprotective results with propofol were obtained when established models of global and focal ischemia were used. In most of these studies, other aspects were addressed in addition to the effects of propofol on neurological and histological outcome. For example, Arcadi et al. (1996) observed that propofol reduced the extent of CA1 injury

TABLE 1. Effects of propofol in experimental models of cerebral ischemia in vivo

Model	Propofol	Histo-pathology	Neurological outcome	Notes (other effects)	Reference
Transient global ischemia					
Cat hypotension (30 min)	31–40 mg/kg/h, i.v.	–	n.t.	Incomplete ischemia	Weir et al. 1989
Rat hypotension + RCCAO (30 min)	2 mg/kg/min, i.v.	+	+	Incomplete ischemia	Kochs et al. 1992
Gerbil 2VO (10 min)	50–100 mg/kg, i.p.	+	n.t.	No effect on survival; postischemic (30 min) administration	Arcadi et al. 1996
Gerbil 2VO (4 min)	50 mg/kg, i.p.	+	n.t.	Mediated by $GABA_A$ receptors	Ito et al. 1999
Gerbil 2VO (4 min)	50–150 mg/kg, i.p.	+	n.t.	↓ MDA	Yamaguchi et al. 2000
Rat 4VO (10 min)	10 mg/kg, i.c.v.	+	n.t.	No effect on CA1 [Glu]e	Yano et al. 2000
Rat hypotension + RCCAO (30 min)	0.8–1.2 mg/kg/min, i.v.	n.t.	n.t.	Incomplete ischemia; ↓ brain [NA] and [Glu]	Engelhard et al. 2003
Rat hypotension + RCCAO (45 min)	0.8–1.2 mg/kg/min, i.v.	+ (28 d after)	n.t.	Incomplete ischemia; ↓ Bax, ↑ Bcl-2, no effect on caspase-3	Engelhard et al. 2004

Continued.

TABLE 1. Continued.

Model	Propofol	Histo-pathology	Neurological outcome	Notes (other effects)	Reference
Focal ischemia					
tMCAO (2 h)	1%, i.v. infusion	–	–	SH rats	Ridenour et al. 1992
pMCAO + tCCAO (1 h)	16 mg/kg/h, i.v.	–	n.t.		Tsai et al. 1994
tMCAO (75 min)	i.v. infusion	+	+	EEG burst suppression dose	Pittman et al. 1997
tMCAO (2 h)	1 mg/kg/min, i.v.	+	n.t.		Young et al. 1997
tMCAO (2 h)	30 mg/kg/h, i.v.	–	n.t.	Pre-ischemic administration	Bhardwaj et al. 2001
tMCAO (1 h)	60 mg/kg/h, i.v.	+ (edema)	n.t.	Hyperglycemic rats; ↓ lactate	Ishii et al. 2002
tMCAO (1 h)	36 mg/kg/h, i.v.	+	n.t.	↓ DA striatal accumulation	Wang et al. 2002
Endothelin 1 injection	25 mg/kg/h, i.v.	+	n.t.	Awake rat model; postischemic (1 h) administration	Gelb et al. 2002
Endothelin 1 injection	25 mg/kg/h, i.v.	+ (3 d after)	+ (21 d after)	Awake rat model; postischemic (2 h) administration	Bayona et al. 2004
pMCAO	100 mg/kg, i.p.	+	± (spontaneous activity only)	Postischemic (30 min) administration	Adembri et al. 2006

Abbreviations: 2VO = two-vessel occlusion; 4VO = four-vessel occulsion; DA = dopamine; Glu = glutamate; MDA = malondialdehyde; NA = noradrenaline; n.t. = not tested; pMCAO = permanent middle cerebral artery occlusion; tCCAO = transient common carotid artery occlusion; tMCAO = transient middle cerebral artery occlusion; RCCAO = right carotid artery occlusion; SH = spontaneously hypertensive. Symbols: + = neuroprotective; – = not neuroprotective; ± = trend for a neuroprotective effect.

8 days after two-vessel occlusion in gerbils, although it did not affect the rate of animal survival. In the same model, Ito et al. (1999) showed that the effects of propofol were mimicked by midazolam and muscimol and blocked by bicuculline, suggesting a role for $GABA_A$ receptors in the inhibition of neuronal damage, whereas Yamaguchi et al. (2000) reported that propofol attenuated CA1 pyramidal cell death by preventing the production of malondialdehyde, a marker of lipid peroxidation. Propofol was neuroprotective and prevented lipid peroxidation also in the four-vessel occlusion rat model of global ischemia (Ergun et al. 2002), but its effect in this model was not ascribed to a corresponding reduction in the extracellular CA1 concentrations of glutamate (Yano et al. 2000). In rats subjected to transient MCAO, at dose levels causing similar effects on EEG burst suppression, propofol was equivalent to pentobarbital (Pittman et al. 1997) and produced greater protection than isoflurane (Young et al. 1997), suggesting again an action by other mechanisms in addition to $CMRO_2$ depression. However, when administered as a preconditioning agent prior to MCAO occlusion, halothane proved to be more effective than propofol in the attenuation of the infarct volume (Bhardwaj et al. 2001).

Various neurotransmitters have been investigated for their possible contribution to the effects of propofol. Striatal dopamine accumulation was completely abolished by propofol infusion during and after 1-h MCAO in the rat (Wang et al. 2002), whereas propofol and sevoflurane, but not fentanyl/nitrous oxide anesthesia, decreased both norepinephrine and glutamate cerebral concentrations by approximately 60% in a rat model of incomplete ischemia (Engelhard et al. 2003). The effects on glucose metabolism were addressed by Ishii et al. (2002), who showed that high doses of propofol (60 mg/kg/h) attenuated both edema formation (as estimated by nuclear magnetic resonance [NMR] techniques) and lactate accumulation in hyperglycemic rats undergoing transient MCAO.

Because *in vivo* models of cerebral ischemia are typically carried out in anesthetized animals, local intracerebral injections of the potent vasoconstrictor endothelin-1 were used to induce focal ischemia in the awake rat (Gelb et al. 2002). Under these conditions, 25 mg/kg/h propofol was neuroprotective even when administered 1 h after stroke induction. In a subsequent study, the same group demonstrated that a propofol infusion period of 3 h, even when delayed for 2 h after the endothelin-1 injection, reduced the infarct size when observed 3 days but not 21 days after ischemia (Bayona et al. 2004). On the other hand, motor function improvements (using the Montoya staircase test) were evident even at the latest time-point in their study. The issue of long-term neuroprotection with propofol was also addressed by Engelhard et al. (2004) in their model of incomplete hemispheric ischemia combined with hemorrhagic hypotension, demonstrating that propofol reduced neuronal damage for at least 28 days. It should be noted, however, that this model appears to be particularly mild, given that propofol-treated rats displayed no residual injury after ischemia. In a recent study, Adembri et al. (2006) were able to demonstrate neuroprotection with propofol also in a rat model of permanent MCAO: the infarct volume was reduced by approximately 30% when administered up to 30 min after the occlusion. Protection was particularly evident in the most anterior brain areas, including the frontoparietal cortex, where a network of surface collateral connections exists and thus ischemic neuronal damage (and the ensuing impairment of spontaneous activity) is more likely to be salvaged by pharmacologic intervention. The high dose of propofol used in this study (100 mg/kg, i.p.) was perhaps justified by the severity of the model, and in any case it should be taken into account that in most other studies propofol was used at lower doses but administered for hours by continuous infusion.

In Vitro Experimental Models of Cerebral Ischemia

In vitro models of cerebral ischemia are often exploited as preliminary screening approaches in the quest for novel neuroprotective agents. However, in the case of propofol, they have been basically used to confirm *in vivo* findings or to shed a clearer light on its possible mechanism of action (Table 2).

As for the *in vivo* studies, initial experiments with propofol *in vitro* were carried out using widely variable doses (0.05–160 μM, see Table 2) and nonconventional simulations of cerebral ischemia, such as fresh hippocampal slices prepared from adult rats and immediately exposed to brief periods (5–10 min) of anoxia or oxygen-glucose deprivation (OGD). When a reduction in the amplitude of CA1 pyramidal cell layer population spikes was used as an index of "ischemic" neurotransmission damage, propofol was able to improve its recovery only under hyperthermic (39°C) conditions, possibly due to its effects on Ca^{2+} influx and on Na^{+} and K^{+} levels at this temperature (Amorim et al. 1995). The negative effects of 100 μM propofol on CA1 population spikes at 37°C were related to its inability to reduce the NMDA-mediated $[Ca^{2+}]_i$ response in the pyramidal cell layer (Zhan et al. 2001). In a similar study by the same group, thiopental, but not propofol, was able to reduce cell swelling, as revealed by light transmittance and CA1 pyramidal cell expansion, immediately after a brief (10 min) OGD (Qi et al. 2002).

Brain cells or slices prepared from embryonic or neonatal rat tissue can be cultured for weeks *in vitro*, allowing for more prolonged exposures (30–90 min) to OGD and assessment of delayed neuronal damage after adequate periods (at least 24 h) of reoxygenation. In mixed cortical cell cultures exposed to 90-min OGD, clinically relevant concentrations of propofol (0.05–10 μM) afforded neuroprotection, as observed 24 h later, equivalent to that of the NMDA antagonist MK-801 (Velly et al. 2003). In this study, propofol was able to restore the increase in glutamate extracellular concentrations and the decrease of glutamate uptake induced by OGD via a GLT1-independent mechanism. In organotypic hippocampal slice cultures exposed to 1-h OGD, mild hypothermia (35°C) attenuated OGD injury in CA1, CA3, and dentate neurons, whereas propofol, at concentrations (10–100 μM) that reduced glutamate and NMDA receptor responses in cortical and hippocampal neurons, could only protect the dentate gyrus (Feiner et al. 2005). In a more recent organotypic hippocampal slice study, in which a shorter (30 min) exposure to OGD induced selective CA1 injury as occurs *in vivo*, propofol (10–100 μM) reduced pyramidal cell death, possibly by preventing an increase in neuronal mitochondrial swelling (Adembri et al. 2006). Similarly, in hippocampal cell cultures exposed to OGD, propofol attenuated neuronal death 3 h after OGD and prevented the depolarization of the mitochondrial membrane potential, without reducing the number of TUNEL-positive neurons (Iijima et al. 2006). Hence, it appears that propofol may block early necrosis *in vitro* but not subsequent apoptosis, which is in agreement with the lack of long-term histological protection *in vivo*, particularly if the ischemic insult is severe. However, this postponement of neuronal death afforded by propofol may be of importance to permit intervention with other decisive pharmacologic strategies.

NEUROPROTECTION WITH PROPOFOL IN EXPERIMENTAL MODELS OF TRAUMATIC BRAIN INJURY

As compared with studies in models of cerebral ischemia, there are relatively fewer reports on the effects of propofol in experimental traumatic brain injury. A first *in vitro* study

TABLE 2. Effects of propofol in experimental models of cerebral ischemia in vitro

Model	Propofol	Neuroprotection	Notes (other effects)	References
Fresh hippocampal slices				
Anoxia (5–7 min)	20 μg/mL	+ (CA1 population spikes)	Prevents changes in Ca^{2+}, Na^{+}, and K^{+}; effects seen at 39°C but not at 37°C	Amorim et al. 1995
OGD (4–7.5 min)	100 μM	– (CA1 population spikes)	↑ NMDA-mediated ↑ in $[Ca^{2+}]_i$	Zhan et al. 2001
OGD (10 min)	160 μM	– (cell swelling)		Qi et al. 2002
Mixed cortical cell cultures				
OGD (90 min)	0.05–10 μM	+ (LDH release)	Prevents ↑ $[Glu]_e$; restores glutamate uptake	Velly et al. 2003
Organotypic hippocampal slice cultures				
OGD (60 min)	10–100 μM	± (PI staining, dentate gyrus only)	↓ Glutamate and NMDA responses in cortical and hippocampal neurons	Feiner et al. 2005
OGD (30 min)	10–100 μM	+ (PI staining)	Prevents mitochondrial swelling	Adembri et al. 2006
Hippocampal cell cultures				
OGD (90 min)	1 μM	+ (EthD-1 staining)	Prevents depolarization of MMP; no effect on TUNEL-positive cells	Iijima et al. 2006

Abbreviations: EthD-1 = ethidium homodimer; LDH = lactate dehydrogenase; MMP = mitochondrial membrane potential; OGD = oxygen-glucose deprivation; PI = propidium iodide. Symbols: + = neuroprotective; – = not neuroprotective ; ± = trend for a neuroprotective effect.

in fresh hippocampal slices showed that propofol promotes acute granule cell survival if applied before and during the mechanical amputation of their dendrites, by potentiating pre- and postsynaptic $GABA_A$-mediated inhibitory transmission (Hollrigel et al. 1996). Subsequent *in vivo* studies, however, have led to less encouraging results, presumably because the histopathological outcome has consistently been examined too early after the induction of traumatic injury. In a weight drop model of spinal cord injury in the rat, a single intraperitoneal (i.p.) dose of propofol (at 15 or 40 mg/kg) induced significant attenuation of lipid peroxidation but no ultrastructural improvement 1 h after trauma (Kaptanoglu et al. 2002). Similarly, propofol (100 mg/kg, i.p.) prevented the increases in malondialdehyde and nitric oxide serum levels 24 h after closed head injury in rats (Ozturk et al. 2005) but was unable, at doses that maintained EEG burst-suppression ratios of 1–5% and 30–40%, to ameliorate histopathological damage and caspase-3 levels 6 h after controlled cortical impact in rats (Eberspacher et al. 2006). Interestingly, in a similar model propofol was associated with a poor motor function outcome 1–5 days after trauma, but shared the same beneficial properties as other sedative/anesthetics on posttraumatic cognitive testing and histological analysis at 18 and 21 days, respectively (Statler et al. 2006). Nevertheless, as discussed by the authors of the latter study, the scientific literature still lacks scrupulous publications reporting the results of studies aimed at elucidating the precise effects of anesthetics on posttraumatic injury cascades and outcomes.

MECHANISMS OF THE NEUROPROTECTIVE EFFECTS OF PROPOFOL

Most anesthetic agents are neuroprotective because of their ability to reduce the $CMRO_2$, which has a beneficial impact on the balance between brain energy supply and demand, and because they increase neuronal tolerance to hypoxic/ischemic injury. However, it appeared quite soon evident that propofol has no direct preconditioning effect (see for review Hans and Bonhomme 2006) and that cerebral metabolic depression cannot entirely account for its effects in experimental ischemia, suggesting that there might be other mechanisms playing a key role in propofol-mediated neuroprotection (Todd and Warner 1992) (Fig. 2).

Propofol has been proposed to attenuate glutamate-mediated excitotoxic mechanisms by either decreasing NMDA receptor activation, reducing glutamate release, or recovering the function of transporters responsible for glutamate uptake into neuronal and glial cells. The antagonism exerted by propofol on NMDA receptors, however, is rather weak. Propofol at clinical concentrations (35 μM) displays only a slight inhibition (by $\sim$30%) of NMDA receptors expressed on *Xenopus* oocytes (Yamakura et al. 1995), whereas its IC_{50} on NMDA responses in cultured mouse neurons is quite high (160 μM) (Orser et al. 1995). Hence, it is not surprising that propofol was able to protect cultured hippocampal neurons against NMDA toxicity (Hans et al. 1994), but displayed either a lack of protection in primary cortical cell cultures (Shibuta et al. 2001) or a worsening of NMDA toxicity (Zhu et al. 1997) and NMDA-mediated $[Ca^{2+}]_i$ responses (Zhan et al. 2001) in hippocampal slices. Moreover, Feiner et al. (2005) showed that the reduction of glutamate and NMDA receptor responses exerted by propofol in cortical and hippocampal neurons was not associated with an attenuation of OGD injury and excitotoxicity in organotypic hippocampal slices. Propofol has also been shown to modulate glutamate release: although the hypoxia-evoked

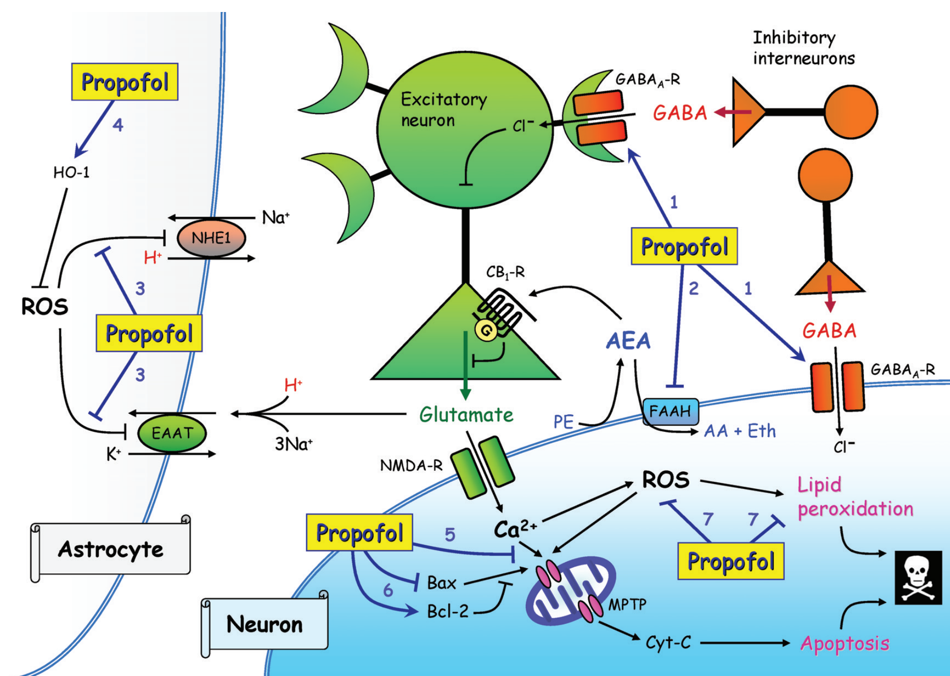

FIG. 2. Schematic model providing a possible explanation for the neuroprotective effects of propofol. Following acute cerebral injury, excessive release and reduced glial uptake of glutamate activates NMDA receptors and produces a sustained influx of Ca^{2+} in neurons. The rapid buildup of intracellular Ca^{2+} promotes the deleterious formation of reactive oxygen species (ROS) and lipid peroxidation and, on the other hand, leads to the opening of the mitochondrial membrane permeability transition pore (MPTP), release of cytochrome C (Cyt-C) into the cytosol, and apoptotic cell death. Propofol can interfere with these toxic mechanisms at many levels: (1) by directly activating $GABA_A$ receptors, thus potentiating the inhibitory effects of GABA on excitatory postsynaptic neurons and on glutamate release; (2) by inibiting the fatty acid amide hydrolase (FAAH), thereby increasing the levels of endocannabinoids like anandamide (AEA) and their action on presynaptic CB1 receptors that exert an inhibitory control on glutamate release; (3) by preventing the inhibitory effects of ROS on astrocytic high-affinity glutamate transporters (EAAT) and on the Na^+/H^+ exchanger (NHE1) that regulates intracellular pH and the efficiency of EAAT; (4) by increasing the expression of the antioxidant enzyme heme oxygenase 1 (HO-1) in astrocytes; (5) by preventing mitochondrial swelling caused by acute overload of Ca^{2+}; (6) by preventing the elevation of the proapoptotic factor Bax and increasing the concentrations of the antiapoptotic factor Bcl-2; and (7) by directly scavenging ROS and inhibiting lipid peroxidation. Other abbreviations: AA = arachidonic acid; Eth = ethanolamine; PE = phosphatidylethanolamine.

release of glutamate from cortical slices does not appear to be affected (Bickler et al. 1995), both the Na^+ channel–dependent release from isolated nerve terminals (Ratnakumari and Hemmings, Jr. 1997; Lingamaneni et al. 2001) and the K^+-evoked glutamate output from cerebrocortical slices (Buggy et al. 2000) are inhibited by propofol. In addition, propofol does not alter high-affinity glutamate uptake by brain synaptosomes under standard conditions (Nicol et al. 1995) but is able to normalize glutamate transport in astrocytes during oxidative stress (Sitar et al. 1999; Peters et al. 2001) and in cortical neurons exposed to OGD (Velly et al. 2003). Altogether, these effects on glutamate release and uptake were predicted to result in a decrease in the brain extracellular concentrations of glutamate to nonexcitotoxic levels. In a first study, however, i.c.v. administration of propofol was neuroprotective against global ischemia, but the parallel reduction in extracellular glutamate

was ascribed to the intralipid vehicle (Yano et al. 2000). More recent studies were eventually able to demonstrate that propofol effectively reduces glutamate extracellular concentrations in models of ischemia *in vitro* (Velly et al. 2003) and *in vivo* (Engelhard et al. 2003).

A mechanism that is known to be beneficial against acute neuronal injury is the potentiation of GABAergic neuronal activity, mainly due to its counteracting effects on excitatory neurotoxicity. Propofol directly activates $GABA_A$ receptors (Williams and Akabas 2002), leading to neuronal hyperpolarization and enhancement of inhibitory synaptic transmission (Concas et al. 1991; Orser et al. 1994, 1995). Bicuculline completely reversed the inhibition of evoked CA1 population spikes induced by propofol in hippocampal slices (Wakasugi et al. 1999) and blocked the neuroprotective effects of propofol in granule cells after dendrotomy (Hollrigel et al. 1996) or in gerbils subjected to global ischemia (Ito et al. 1999). In a number of occasions, propofol's inhibitory effects on glutamate transmission have been reported to be indirectly mediated by $GABA_A$ receptors, such as the reduction of K^+-evoked glutamate release from cerebrocortical slices that was blocked by bicuculline (Buggy et al. 2000) and the inhibition of glutamate receptor responses that was removed by picrotoxin in cortical and hippocampal neurons (Feiner et al. 2005).

Free radical generation is an important component of neurologic injury. Propofol has been assumed to possess antioxidant activity because it bears a phenolic OH group like the natural lipid peroxidation inhibitor α-tocopherol (vitamin E). Indeed, propofol has repeatedly been demonstrated to inhibit free radical generation, prevent the initiation of free radical chain reactions, and terminate their propagation by scavenging highly reactive species and inhibiting lipid peroxidation (see for review, Wilson and Gelb 2002). In particular, propofol reduced the production of the lipid peroxidation marker malondialdehyde following transient forebrain ischemia in gerbils (Yamaguchi et al. 2000) and rats (Ergun et al. 2002) as well as in experimental models of spinal cord injury (Kaptanoglu et al. 2002) and closed head injury (Ozturk et al. 2005) in rats. In astrocyte primary cultures, propofol prevented the inhibitory effects of the oxidant *tert*-butyl hydroperoxide (*t*-BOOH) on glutamate uptake and retention (Sitar et al. 1999; Peters et al. 2001) and on the Na^+/H^+ exchanger, which regulates intracellular pH and the efficiency of the high-affinity glutamate transporter (Daskalopoulos et al. 2001). However, in this experimental system, propofol had contradictory effects on astrocytic ascorbate and was unable to prevent the loss of glutathione induced by *t*-BOOH (Daskalopoulos et al. 2001; Bayona et al. 2004). Recently, a novel antioxidant mechanism has been proposed, in which propofol attenuates the effects of peroxynitrite oxidative stress in cultured astrocytes by increasing the expression of heme oxygenase-1 (Acquaviva et al. 2004).

Following acute brain injury, oxidative stress can lead to neuronal death by triggering a number of detrimental cellular responses, including the loss of selective ion permeability in mitochondria, which appears to be one of the regulators of the apoptotic cascade (Mattson and Kroemer 2003). As discussed earlier, however, propofol appears to prevent necrotic rather than apoptotic cell death in experimental cerebral ischemia (Iijima et al. 2006). Acquaviva et al. (2004) showed that propofol attenuated peroxynitrite-mediated caspase-3 activation in astrocytes, but this apoptotic marker was not modified by propofol after incomplete cerebral ischemia in rats (Engelhard et al. 2004). In the latter study, other apoptotic mechanisms like the elevation of Bax and the reduction of Bcl-2 were prevented by propofol at various time-points up to 7 days after ischemia, but not 28 days later (Engelhard et al. 2004). On the other hand, propofol has been demonstrated to prevent mitochondrial swelling caused by acute overload of Ca^{2+} in isolated brain mitochondria or by OGD injury

in organotypic hippocampal slices (Adembri et al. 2006). Similarly, the OGD-induced depolarization of mitochondrial membrane potential was prevented by propofol in hippocampal neuronal cultures (Iijima et al. 2006). It is not known at present whether propofol acts directly on mitochondria or, indirectly, by modulating the production and concentrations of other cytotoxic mediators (i.e., free radicals, glutamate, and intracellular Ca^{2+}) that can trigger multiple downstream cascades that lead to the opening of the mitochondrial permeability transition pore and to apoptotic neuronal death.

Very recently, propofol has been shown to interact with the endocannabinoid system in the brain. This novel mechanism has been associated with the sedative, psychomimetic, and antiemetic properties of propofol, but there is accumulating evidence that the endocannabinoid system regulates the release of various neurotransmitters and may also be involved in neuroprotection (van der Stelt and Di Marzo 2005). Specifically, propofol (at 10–100 μM *in vitro*) has been demonstrated to inhibit one of the enzymes catalyzing endocannabinoid hydrolysis and inactivation, the fatty acid amide hydrolase, thereby enhancing at sedating doses (100 mg/kg, i.p.) the brain levels of the endogenous endocannabinoids AEA and 2-arachidonoylglycerol in mouse brain *in vivo* (Patel et al. 2003). The CB1 endocannabinoid receptor appeared to contribute to the sedative effects of propofol in this study. Interestingly, whereas the use of sevoflurane in humans resulted in a decrease of whole blood AEA levels, total intravenous anesthesia with propofol produced a slight increase in AEA concentrations (Schelling et al. 2006).

NEUROPROTECTION IN THE CLINICAL SETTING

Even molecules that have shown to be dramatically neuroprotective under experimental conditions may not have clinical utility if they are endowed with negative effects on cerebral physiology, especially on ICP and on the coupling between CBF and $CMRO_2$. The effects of propofol on cerebral physiology are generally positive. In contrast to volatile anesthetic agents, which cause a dose-dependent increase in CBF with the risk of increasing ICP, propofol *always* reduces CBF and ICP (Kaisti et al. 2002; Ludbrook et al. 2002). The effect on CBF is mostly mediated by the reduction of $CMRO_2$, even if a direct vasoconstrictor effect is also thought to contribute, as the decrease in CBF is larger than that in $CMRO_2$ (Cenic et al. 2002). Despite direct vasoconstriction, coupling is substantially preserved (Newman et al. 1995). Propofol reduces ICP, a property that is mandatory in case of intracranial hypertension and is always favorable in cases of acute brain injury. Cerebral autoregulation and CO_2 responsiveness are maintained during propofol anesthesia (Fox et al. 1992), and an anticonvulsant activity comparable to that of thiopental has also been described (Walder et al. 2002). Other specific advantages in the use of propofol in neurosurgery include a rapid recovery when intraoperative awake functional evaluation is requested, a lower incidence of nausea and vomiting as compared to volatile anesthetics (Gupta et al. 2004), a lesser degree of depression of electrophysiological brain activity as compared to all the other anesthetic agents, which allows better intraoperative monitoring (Boisseau et al. 2002). Finally, there is now relatively clear evidence of postoperative cognitive dysfunction after major noncardiac surgery, especially in the elderly. However, general anesthetics (both inhalational and intravenous) seem not to play a causative role (Newmann et al. 2007).

Despite the great number of experimental studies indicating that propofol is neuroprotective and its manifold positive effects on cerebral physiology when administered in the

clinical setting, there are no data in the literature showing that the use of propofol improves the neurological outcome following acute cerebral injury in patients. Several factors may have contributed to this. First, the neuroprotective effects of propofol on spontaneous stroke and on head trauma have never been specifically assessed in randomized clinical trials, most likely because propofol, like all other drugs tested so far in clinical trials with the exception of recombinant tissue plasminogen activator (De Keyser et al. 1999; Khaja and Grotta 2007), does not appear from experimental studies to possess the ability to be a *neuroresuscitative* drug. Second, most of the studies with propofol in humans were performed during surgery, evaluating the possible neuroprotective effects of propofol not *per se* but always in comparison with other anesthetic regimens, often using small numbers of patients and disparate (and frequently nonrelated) end-points of neuroprotection (cognitive assessment, cerebral O_2 content, and biochemical markers).

At present, there is no clear evidence that propofol may offer specific neuroprotective advantages in cardiac or brain surgery as compared to volatile anesthetics.

Neuroprotection During Cardiac Surgery

Because cardiac surgery with cardiopulmonary bypass is complicated by permanent neurological sequelae in a high percentage of patients, most of the clinical studies investigating the potential neuroprotective effects of propofol were conducted in cardiac surgery settings. Mostly, studies were aimed at evaluating whether propofol was able to mitigate the episodes of jugular vein O_2 saturation ($SjvO_2$) under the threshold of ischemia ($SjvO_2 < 50\%$) that frequently occur during cardiac surgery with bypass (Cook et al. 1994). Propofol was not able to reduce $SjvO_2$ desaturation in some studies (Souter et al. 1998; Nandate et al. 2000), whereas in another study the number of episodes of desaturation and their durations were shown to be reduced with propofol as compared with fentanyl anesthesia (Kadoi et al. 2003). In a small study in 20 patients undergoing coronary artery bypass grafting, propofol anesthesia, but not isoflurane anesthesia, was associated with a surprising increase in the plasmatic protein S-100β, a marker of cerebral injury (Kanbak et al. 2004). However, extracerebral potential sources of S-100β exist (Stocchetti 2005), and the neurological outcome in propofol-treated patients was similar to that observed in the control group treated with isoflurane. Therefore, it is questionable whether slight differences in $SvjO_2$ and in biochemical markers translate into differences in clinical outcome, taking also in consideration that the intraoperative use of propofol has never been reported to be correlated with a deterioration of the neurological outcome.

Use of Propofol in Neurosurgery

As for cardiac surgery, no clinical trial has demonstrated that propofol ameliorates the outcome in neurosurgery (Magni et al. 2005). Therefore, the debate remains hot about the best anesthetic in neurosurgery. On one hand, propofol has been suggested as the best anesthetic in patients undergoing brain tumor removal because it maintains cerebral perfusion pressure better than isoflurane or sevoflurane (Petersen et al. 2003). On the other hand, reports showing that during neurosurgical anesthesia propofol episodes of $SjvO_2$ below the critical threshold of 50% do occur (Cenic et al. 2002; Chieregato et al., 2003), had raised concerns about its safety, even though the clinical outcome in neurosurgical patients was

never reported to be altered (Munoz et al. 2002). A recent study by Rasmussen et al. (2004) has directly addressed the question, showing that propofol anesthesia may be associated with a $SjvO_2$ below the ischemic threshold, but there is no evidence of cerebral ischemia, as detected by NMR. Therefore, taking in consideration its positive effects on cerebral physiology, propofol not only is safe during neurosurgery but probably is the anesthetic of choice in many conditions.

CONCLUSIONS

Taken as a whole, the available data appear to indicate that propofol anesthesia, as compared to the awake state, has the potential of offering a certain degree of neuroprotection, which is not exclusively due to reduction of the $CMRO_2$ but involves inhibition and/or modulation of specific cellular pathways activated following acute brain injury. At present, however, there are no clinical data available to indicate that propofol may have *neuro-resuscitative* properties (Koerner and Brambrink 2006), as it occurs with other anesthetic agents with the possible exception of xenon (Preckel et al. 2006). It is probably quite naïve to imagine that a single anesthetic, given for a limited amount of time, might offer long-lasting protection against cerebral injuries for which an evolution of days and months after the primary insult occurs. On the other hand, propofol may share a useful role with other anesthetics in the prevention of intraoperative ischemic insults, which tend to be less severe than spontaneous strokes. Undoubtedly, propofol offers advantages during neurosurgery in which intracranial hypertension is a menace, in that it allows the surgeon to operate under safe and optimal conditions (Hans and Bonhomme 2006).

REFERENCES

Acquaviva R, Campisi A, Murabito P, Raciti G, Avola R, Mangiameli S, Musumeci I, Barcellona ML, Vanella A, Li VG (2004) Propofol attenuates peroxynitrite-mediated DNA damage and apoptosis in cultured astrocytes: An alternative protective mechanism. *Anesthesiology 101*:1363–1371.

Adembri C, Venturi L, Tani A, Chiarugi A, Gramigni E, Cozzi A, Pancani T, De Gaudio RA, Pellegrini-Giampietro DE (2006) Neuroprotective effects of propofol in models of cerebral ischemia: Inhibition of mitochondrial swelling as a possible mechanism. *Anesthesiology 104*:80–89.

Amorim P, Chambers G, Cottrell J, Kass IS (1995) Propofol reduces neuronal transmission damage and attenuates the changes in calcium, potassium, and sodium during hyperthermic anoxia in the rat hippocampal slice. *Anesthesiology 83*:1254–1265.

Arcadi FA, Rapisarda A, De Luca R, Trimarchi GR, Costa G (1996) Effect of 2,6-diisopropylphenol on the delayed hippocampal cell loss following transient forebrain ischemia in the gerbil. *Life Sci 58*:961–970.

Baker MT, Naguib M (2005) Propofol: The challenges of formulation. *Anesthesiology 103*:860–876.

Bayona NA, Gelb AW, Jiang Z, Wilson JX, Urquhart BL, Cechetto DF (2004) Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. *Anesthesiology 100*:1151–1159.

Bhardwaj A, Castro III AF, Alkayed NJ, Hurn PD, Kirsch JR (2001) Anesthetic choice of halothane versus propofol: Impact on experimental perioperative stroke. *Stroke 32*:1920–1925.

Bickler PE, Buck LT, Feiner JR (1995) Volatile and intravenous anesthetics decrease glutamate release from cortical brain slices during anoxia. *Anesthesiology 83*:1233–1240.

Boisseau N, Madany M, Staccini P, Armando G, Martin F, Grimaud D, Raucoules-Aime M (2002) Comparison of the effects of sevoflurane and propofol on cortical somatosensory evoked potentials. *Br J Anaesth 88*:785–789.

Borgeat A, Wilder-Smith OH, Saiah M, Rifat K (1992) Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology 76*:510–512.

Borgeat A, Wilder-Smith O, Forni M, Suter PM (1994) Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. *Can J Anaesth 41*:1117–1119.

Briggs LP, Clarke RS, Watkins J (1982) An adverse reaction to the administration of disoprofol (Diprivan). *Anaesthesia 37*:1099–1101.

Bryson HM, Fulton BR, Faulds D (1995) Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs 50*:513–559.

Buggy DJ, Nicol B, Rowbotham DJ, Lambert DG (2000) Effects of intravenous anesthetic agents on glutamate release: A role for $GABA_A$ receptor-mediated inhibition. *Anesthesiology 92*:1067–1073.

Cenic A, Craen RA, Lee TY, Gelb AW (2002) Cerebral blood volume and blood flow responses to hyperventilation in brain tumors during isoflurane or propofol anesthesia. *Anesth Analg 94*:661–666.

Chieregato A, Calzolari F, Trasforini G, Targa L, Latronico N (2003) Normal jugular bulb oxygen saturation. *J Neurol Neurosurg Psychiatry 74*:784–786.

Concas A, Santoro G, Serra M, Sanna E, Biggio G (1991) Neurochemical action of the general anaesthetic propofol on the chloride ion channel coupled with GABAA receptors. *Brain Res 542*:225–232.

Cook DJ, Oliver WC, Jr., Orszulak TA, Daly RC (1994) A prospective, randomized comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg 107*:1020–1028.

Daskalopoulos R, Korcok J, Farhangkhgoee P, Karmazyn M, Gelb AW, Wilson JX (2001) Propofol protection of sodium-hydrogen exchange activity sustains glutamate uptake during oxidative stress. *Anesth Analg 93*:1199–1204.

De Keyser J, Sulter G, Luiten PG (1999) Clinical trials with neuroprotective drugs in acute ischaemic stroke: Are we doing the right thing? *Trends Neurosci 22*:535–540.

Eberspacher E, Heimann K, Hollweck R, Werner C, Schneider G, Engelhard K (2006) The effect of electroencephalogram-targeted high- and low-dose propofol infusion on histopathological damage after traumatic brain injury in the rat. *Anesth Analg 103*:1527–1533.

Engelhard K, Werner C, Eberspacher E, Pape M, Stegemann U, Kellermann K, Hollweck R, Hutzler P, Kochs E (2004) Influence of propofol on neuronal damage and apoptotic factors after incomplete cerebral ischemia and reperfusion in rats: A long-term observation. *Anesthesiology 101*:912–917.

Engelhard K, Werner C, Hoffman WE, Matthes B, Blobner M, Kochs E (2003) The effect of sevoflurane and propofol on cerebral neurotransmitter concentrations during cerebral ischemia in rats. *Anesth Analg 97*:1155–1161.

Ergun R, Akdemir G, Sen S, Tasci A, Ergungor F (2002) Neuroprotective effects of propofol following global cerebral ischemia in rats. *Neurosurg Rev 25*:95–98.

Feiner JR, Bickler PE, Estrada S, Donohoe PH, Fahlman CS, Schuyler JA (2005) Mild hypothermia, but not propofol, is neuroprotective in organotypic hippocampal cultures. *Anesth Analg 100*:215–225.

Fox J, Gelb AW, Enns J, Murkin JM, Farrar JK, Manninen PH (1992) The responsiveness of cerebral blood flow to changes in arterial carbon dioxide is maintained during propofol-nitrous oxide anesthesia in humans. *Anesthesiology 77*:453–456.

Fulton B, Sorkin EM (1995) Propofol: An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. *Drugs 50*:636–657.

Gelb AW, Bayona NA, Wilson JX, Cechetto DF (2002) Propofol anesthesia compared to awake reduces infarct size in rats. *Anesthesiology 96*:1183–1190.

Gupta A, Stierer T, Zuckerman R, Sakima N, Parker SD, Fleisher LA (2004) Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: A systematic review. *Anesth Analg 98*:632–641.

Hans P, Bonhomme V (2006) Why we still use intravenous drugs as the basic regimen for neurosurgical anaesthesia. *Curr Opin Anaesthesiol 19*:498–503.

Hans P, Bonhomme V, Collette J, Albert A, Moonen G (1994) Propofol protects cultured rat hippocampal neurons against N-methyl-D-aspartate receptor-mediated glutamate toxicity. *J Neurosurg Anesthesiol 6*:249–253.

Hollrigel GS, Toth K, Soltesz I (1996) Neuroprotection by propofol in acute mechanical injury: Role of GABAergic inhibition. *J Neurophysiol 76*:2412–2422.

Iijima T, Mishima T, Akagawa K, Iwao Y (2006) Neuroprotective effect of propofol on necrosis and apoptosis following oxygen-glucose deprivation: Relationship between mitochondrial membrane potential and mode of death. *Brain Res 1099*:25–32.

Ishii H, Arai T, Segawa H, Morikawa S, Inubushi T, Fukuda K (2002) Effects of propofol on lactate accumulation and oedema formation in focal cerebral ischaemia in hyperglycaemic rats. *Br J Anaesth 88*:412–417.

Ito H, Watanabe Y, Isshiki A, Uchino H (1999) Neuroprotective properties of propofol and midazolam, but not pentobarbital, on neuronal damage induced by forebrain ischemia, based on the GABAA receptors. *Acta Anaesthesiol Scand 43*:153–162.

James R, Glen JB (1980) Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. *J Med Chem 23*:1350–1357.

Kadoi Y, Saito S, Kunimoto F, Goto F, Fujita N (2003) Comparative effects of propofol versus fentanyl on cerebral oxygenation state during normothermic cardiopulmonary bypass and postoperative cognitive dysfunction. *Ann Thorac Surg 75*:840–846.

Kaisti KK, Metsahonkala L, Teras M, Oikonen V, Aalto S, Jaaskelainen S, Hinkka S, Scheinin H (2002) Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. *Anesthesiology 96*:1358–1370.

Kanbak M, Saricaoglu F, Avci A, Ocal T, Koray Z, Aypar U (2004) Propofol offers no advantage over isoflurane anesthesia for cerebral protection during cardiopulmonary bypass: A preliminary study of S-100beta protein levels. *Can J Anaesth 51*:712–717.

Kanto J, Gepts E (1989) Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet 17*:308–326.

Kaptanoglu E, Sen S, Beskonakli E, Surucu HS, Tuncel M, Kilinc K, Taskin Y (2002) Antioxidant actions and early ultrastructural findings of thiopental and propofol in experimental spinal cord injury. *J Neurosurg Anesthesiol 14*:114–122.

Kawaguchi M, Furuya H, Patel PM (2005) Neuroprotective effects of anesthetic agents. *J Anesth 19*:150–156.

Kay B, Rolly G (1977) I.C.I. 35868, a new intravenous induction agent. *Acta Anaesthesiol Belg 28*:303–316.

Khaja AM, Grotta JC (2007) Established treatments for acute ischaemic stroke. *Lancet 369*:319–330.

Kochs E, Hoffman WE, Werner C, Thomas C, Albrecht RF, Schulte am Esch J (1992) The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage following incomplete ischemia in rats. *Anesthesiology 76*:245–252.

Koerner IP, Brambrink AM (2006) Brain protection by anesthetic agents. *Curr Opin Anaesthesiol 19*:481–486.

Lingamaneni R, Birch ML, Hemmings HC, Jr. (2001) Widespread inhibition of sodium channel-dependent glutamate release from isolated nerve terminals by isoflurane and propofol. *Anesthesiology 95*:1460–1466.

Liu LL, Gropper MA (2003) Postoperative analgesia and sedation in the adult intensive care unit: A guide to drug selection. *Drugs 63*:755–767.

Ludbrook GL, Visco E, Lam AM (2002) Propofol: Relation between brain concentrations, electroencephalogram, middle cerebral artery blood flow velocity, and cerebral oxygen extraction during induction of anesthesia. *Anesthesiology 97*:1363–1370.

Magni G, Baisi F, La RI, Imperiale C, Fabbrini V, Pennacchiotti ML, Rosa G (2005) No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanyl in patients undergoing craniotomy for supratentorial intracranial surgery. *J Neurosurg Anesthesiol 17*:134–138.

Mattson MP, Kroemer G (2003) Mitochondria in cell death: novel targets for neuroprotection and cardioprotection. *Trends Mol Med 9*:196–205.

Michenfelder JD, Theye RA (1973) Cerebral protection by thiopental during hypoxia. *Anesthesiology 39*:510-517.

Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard RA (2001) The effects of small-dose ketamine on propofol sedation: Respiration, postoperative mood, perception, cognition, and pain. *Anesth Analg 92*:1465–1469.

Munoz HR, Nunez GE, de la Fuente JE, Campos MG (2002) The effect of nitrous oxide on jugular bulb oxygen saturation during remifentanyl plus target-controlled infusion propofol or sevoflurane in patients with brain tumors. *Anesth Analg 94*:389–392, table.

Nandate K, Vuylsteke A, Ratsep I, Messahel S, Oduro-Dominah A, Menon DK, Matta BF (2000) Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery. *Br J Anaesth 84*:631–633.

Newman MF, Murkin JM, Roach G, Croughwell ND, White WD, Clements FM, Reves JG (1995) Cerebral physiologic effects of burst suppression doses of propofol during nonpulsatile cardiopulmonary bypass. CNS Subgroup of McSPI. *Anesth Analg 81*:452–457.

Newman S, Stygall J, Hirani S, Shaefi S, Maze M (2007) Postoperative cognitive dysfunction after noncardiac surgery: A systematic review. *Anesthesiology 106*:572–590.

Nicol B, Rowbotham DJ, Lambert DG (1995) Glutamate uptake is not a major target site for anaesthetic agents. *Br J Anaesth 75*:61–65.

Orser BA, Wang LY, Pennefather PS, MacDonald JF (1994) Propofol modulates activation and desensitization of $GABA_A$ receptors in cultured murine hippocampal neurons. *J Neurosci 14*:7747–7760.

Orser BA, Bertlik M, Wang LY, MacDonald JF (1995) Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. *Br J Pharmacol 116*:1761–1768.

Ozturk E, Demirbilek S, Kadir BA, Saricicek V, Gulec M, Akyol O, Ozcan EM (2005) Antioxidant properties of propofol and erythropoietin after closed head injury in rats. *Prog Neuropsychopharmacol Biol Psychiat 29*:922–927.

Patel P (2004) No magic bullets: the ephemeral nature of anesthetic-mediated neuroprotection. *Anesthesiology 100*:1049–1051.

Patel S, Wohlfeil ER, Rademacher DJ, Carrier EJ, Perry LJ, Kundu A, Falck JR, Nithipatikom K, Campbell WB, Hillard CJ (2003) The general anesthetic propofol increases brain N-arachidonylethanolamine (anandamide) content and inhibits fatty acid amide hydrolase. *Br J Pharmacol 139*:1005–1013.

Peters CE, Korcok J, Gelb AW, Wilson JX (2001) Anesthetic concentrations of propofol protect against oxidative stress in primary astrocyte cultures: Comparison with hypothermia. *Anesthesiology 94*:313–321.

Petersen KD, Landsfeldt U, Cold GE, Petersen CB, Mau S, Hauerberg J, Holst P, Olsen KS (2003) Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: A randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. *Anesthesiology 98*:329–336.

Pittman JE, Sheng H, Pearlstein R, Brinkhous A, Dexter F, Warner DS (1997) Comparison of the effects of propofol and pentobarbital on neurologic outcome and cerebral infarct size after temporary focal ischemia in the rat. *Anesthesiology 87*:1139–1144.

Preckel B, Weber NC, Sanders RD, Maze M, Schlack W (2006) Molecular mechanisms transducing the anesthetic, analgesic, and organ-protective actions of xenon. *Anesthesiology 105*:187–197.

Qi S, Zhan RZ, Wu C, Fujihara H, Taga K, Shimoji K (2002) The effects of thiopental and propofol on cell swelling induced by oxygen/glucose deprivation in the CA1 pyramidal cell layer of rat hippocampal slices. *Anesth Analg 94*:655–660.

Rasmussen M, Ostergaard L, Juul N, Gyldensted C, Poulsen PV, Cold GE (2004) Do indomethacin and propofol cause cerebral ischemic damage? Diffusion-weighted magnetic resonance imaging in patients undergoing craniotomy for brain tumors. *Anesthesiology 101*:872–878.

Ratnakumari L, Hemmings HC, Jr (1997) Effects of propofol on sodium channel-dependent sodium influx and glutamate release in rat cerebrocortical synaptosomes. *Anesthesiology 86*:428–439.

Ridenour TR, Warner DS, Todd MM, Gionet TX (1992) Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. *Anesthesiology 76*:807–812.

Schelling G, Hauer D, Azad SC, Schmoelz M, Chouker A, Schmidt M, Hornuss C, Rippberger M, Briegel J, Thiel M, et al. (2006) Effects of general anesthesia on anandamide blood levels in humans. *Anesthesiology 104*:273–277.

Shibuta S, Sriranganathan V, Inoue T, Shimizu T, Tomi K, Mashimo T (2001) The effects of propofol on NMDA- or nitric oxide-mediated neurotoxicity in vitro. *NeuroReport 12*:295–298.

Sitar SM, Hanifi-Moghaddam P, Gelb A, Cechetto DF, Siushansian R, Wilson JX (1999) Propofol prevents peroxide-induced inhibition of glutamate transport in cultured astrocytes. *Anesthesiology 90*:1446–1453.

Souter MJ, Andrews PJ, Alston RP (1998) Propofol does not ameliorate cerebral venous oxyhemoglobin desaturation during hypothermic cardiopulmonary bypass. *Anesth Analg 86*:926–931.

Statler KD, Alexander H, Vagni V, Dixon CE, Clark RS, Jenkins L, Kochanek PM (2006) Comparison of seven anesthetic agents on outcome after experimental traumatic brain injury in adult, male rats. *J Neurotrauma 23*:97–108.

Stocchetti N (2005) Brain and sepsis: Functional impairment, structural damage, and markers. *Anesth Analg 101*:1463–1464.

Todd MM, Warner DS (1992) A comfortable hypothesis reevaluated. Cerebral metabolic depression and brain protection during ischemia. *Anesthesiology 76*:161–164.

Tsai YC, Huang SJ, Lai YY, Chang CL, Cheng JT (1994) Propofol does not reduce infarct volume in rats undergoing permanent middle cerebral artery occlusion. *Acta Anaesthesiol Sin 32*:99–104.

Van Der Stelt M, Di Marzo, V (2005) Cannabinoid receptors and their role in neuroprotection. *Neuromol Med 7*:37–50.

Velly LJ, Guillet BA, Masmejean FM, Nieoullon AL, Bruder NJ, Gouin FM, Pisano PM (2003) Neuroprotective effects of propofol in a model of ischemic cortical cell cultures: Role of glutamate and its transporters. *Anesthesiology 99*:368–375.

Wakasugi M, Hirota K, Roth SH, Ito Y (1999) The effects of general anesthetics on excitatory and inhibitory synaptic transmission in area CA1 of the rat hippocampus in vitro. *Anesth Analg 88*:676–680.

Walder B, Tramer MR, Seeck M (2002) Seizure-like phenomena and propofol: A systematic review. *Neurology 58*:1327–1332.

Wang J, Yang X, Camporesi CV, Yang Z, Bosco G, Chen C, Camporesi EM (2002) Propofol reduces infarct size and striatal dopamine accumulation following transient middle cerebral artery occlusion: A microdialysis study. *Eur J Pharmacol 452*:303–308.

Warner DS (2004) Perioperative neuroprotection: are we asking the right questions? *Anesth Analg 98*:563–565.

Weir DL, Goodchild CS, Graham DI (1989) Propofol: effects on indices of cerebral ischemia. *J Neurosurg Anesthesiol* 1:284–289.

Wells BA, Keats AS, Cooley DA (1963) Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. *Surgery 54*:216–223.

Williams DB, Akabas MH (2002) Structural evidence that propofol stabilizes different $GABA_A$ receptor states at potentiating and activating concentrations. *J Neurosci 22*:7417–7424.

Wilson JX, Gelb AW (2002) Free radicals, antioxidants, and neurologic injury: Possible relationship to cerebral protection by anesthetics. *J Neurosurg Anesthesiol 14*:66–79.

Wysowski DK, Pollock ML (2006) Reports of death with use of propofol (Diprivan) for nonprocedural (long-term) sedation and literature review. *Anesthesiology 105*:1047–1051.

Yamaguchi S, Hamaguchi S, Mishio M, Okuda Y, Kitajima T (2000) Propofol prevents lipid peroxidation following transient forebrain ischemia in gerbils. *Can J Anaesth 47*:1025–1030.

Yamakura T, Sakimura K, Shimoji K, Mishina M (1995) Effects of propofol on various AMPA-, kainate- and NMDA-selective glutamate receptor channels expressed in Xenopus oocytes. *Neurosci Lett 188*:187–190.

Yano T, Nakayama R, Ushijima K (2000) Intracerebroventricular propofol is neuroprotective against transient global ischemia in rats: Extracellular glutamate level is not a major determinant. *Brain Res 883*:69–76.

Young Y, Menon DK, Tisavipat N, Matta BF, Jones JG (1997) Propofol neuroprotection in a rat model of ischaemia reperfusion injury. *Eur J Anaesthesiol 14*:320–326.

Zhan RZ, Qi S, Wu C, Fujihara H, Taga K, Shimoji K (2001) Intravenous anesthetics differentially reduce neurotransmission damage caused by oxygen-glucose deprivation in rat hippocampal slices in correlation with N-methyl-D-aspartate receptor inhibition. *Crit Care Med 29*:808–813.

Zhu H, Cottrell JE, Kass IS (1997) The effect of thiopental and propofol on NMDA- and AMPA-mediated glutamate excitotoxicity. *Anesthesiology 87*:944–951.