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# Propofol: an anesthetic possessing neuroprotective effects

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**Abstract. – Propofol is a short-acting intravenous anaesthetic agent and widely used not only in operating rooms but also in the intensive care unit (ICU). Apart from its multiple anaesthetic advantages, the neuroprotective effect of propofol has been demonstrated in diverse models of neuronal injury. The effect of propofol results from activation of gamma-aminobutyric acid (GABA) receptor, modulation excitatory amino acid transmitter system and protecting brain cells against oxidative stress. Moreover, propofol is able to supress apoptosis and inflammation and to regulate neuroprotection-associated proteins or ion homeostasis to act its neuroprotective effects. This review focuses on the research progress of the neuroprotective effects of propofol and its mechanisms of action to date. The implications for possible use for the clinical setting are also discussed.**

*Key Words:*
Propofol, Neuroprotection, Cerebral ischemia, Brain injury.

## Introduction

Propofol (2, 6-disopropylphenol) is an intravenous short-acting anaesthetic agent and has been widely used for induction and maintenance of anesthesia, as well as for sedation[1]. Apart from its use as an anesthetic, propofol exerts a number of non-anaesthetic effects such as antiemetic effects, immunomodulatory activity, anxiolytic effects and analgesia and so on[2,3]. More importantly, it has been demonstrated that propofol acts as an efficacious neuroprotective agent[4] in different models *in vivo*[5-28] such as cerebral ischemia or ischemia-reperfusion (I/R), Parkinson's disease, intracerebral hemorrhage, cerebral resuscitation and ischemia of spinal cords. Moreover, *in vitro* studies have confirmed propofol's neuroprotective properties in different models[29-34]. The clinical data regarding neuroprotective effect of propofol are performed[35]. This article reviews available, up-to-date information on the effects of propofol, one of the most commonly used anaesthetic agents, in terms of neuroprotection and, in particular, discusses the mechanisms of action.

### Chemical Properties

As shown in Figure 1, the empirical formula of propofol is $C_{12}H_{18}O$ and its molecular weight is 178,271. Propofol is highly hydrophobic due to its two isopropylic groups in ortho position with respect to the hydroxyl group, which exerts a steric hindrance that prevents the approach of hydrophilic molecules to the hydroxyl group itself[36]. Therefore, propofol is formulated in a white, oil-in-water emulsion. The currently available preparation is 1% or 2% propofol, 10% soya bean oil, and 1.2% purified egg phospholipid as an emulsifier, with 2.25% of glycerol as a tonicity-adjusting agent, and sodium hydroxide to adjust the pH. To this, 0.005% disodium edetate (EDTA) or sodium metabisulfite is added as antimicrobial agents.

## Mechanisms of Action

### Propofol and GABA

Gamma-aminobutyric acid (GABA) and glycine are critical inhibitory neurotransmitter in the central nervous system (CNS)[37]. Propofol has been proposed to be an anesthesia agent through activating GABA A receptors directly activity[38],


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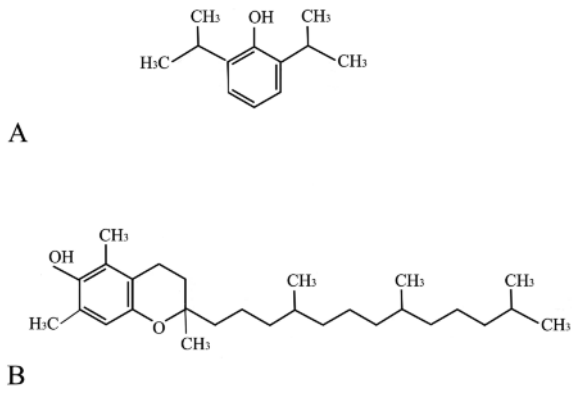


**Figure 1.** The chemical structure of propofol ***(A)*** and Vitamin E ***(B)***.

thereby, slowing the channel-closing time[39] and also acting as a sodium blocker[40]. Activation of GABA A receptors, which include the specific binding subunits for propofol, plays a role in the inhibition of neuronal death induced by brain ischemia[41] and acute mechanical-injury[42]. Moreover, Chen's study showed that propofol can increase GABA accumulation in focal cerebral ischemic areas in reperfusion[20]. Recent research has also suggested that propofol can cause GABA A receptor triggered and subsequent time-dependent neuroprotection in primary cortical neurons[43]. Enhancing the inhibitory effects of GABA, as one of the mechanisms of propofol's anesthetic action, may explain its protective action on the brain.

### Propofol and Antioxidant Property

Reactive oxygen species (ROS) have been implicated in many adult neurodegenerative disorders and other brain dysfunctions such as stroke, trauma, and seizures[44], production of which is a particularly destructive aspect of oxidative stress. Controlling ROS generation or its level may thus hold promise as a standard therapeutic modality for ROS-related neuronal injury. Propofol is similar in chemical structure to the active nucleus of antioxidant substances such as alpha-tocopherol (vitamin E, Figure 1)[45], which has been shown antioxidant ability in different conditions[46]. The clinical studies indicate that propofol increases the antioxidant capacity of plasma in humans[47-49]. As shown by both *in vitro* and *in vivo* studies, propofol can directly scavenge ROS and inhibit free radical generation and lipid peroxidation in various experimental models to protect brain cells against oxidative stress[7,11,50-57].

### Propofol and EAA

Glutamate (Glu) is known as the major excitatory neurotransmitter in the CNS, which exerts its action through ionotropic and metabotropic receptor families such as N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainite receptor[58]. An excess of Glu release and dysfunction of its transporters can induce an accumulation of extracellular Glu, which activates different ionotropic Glu receptors and causes calcium ions to enter cells. The excessive calcium loading plays an important role in neuronal damage[59], which is known as excitotoxicity. Numerous studies have demonstrated that Glu concentration during brain ischemia tended to be attenuated by propofol[20,31,60-62]. Propofol may prevent Glu release from synaptosomes at clinical concentrations, the mechanism of which is attributed to inhibition of presynaptic voltage-dependent $Na^+$ channels by propofol[63-65]. Moreover, the neurological protection of propofol may be due to the defending against oxidative stress-reduced inhibition of Glu clearance[20,31,66-68] and enhancing excitatory amino acid (EAA) transporter 3 activity[69], the effect of which may be PKC-mediated[67]. Propofol was proved to be able to reduce Glu and NMDA receptors responses in cortical and hippocampal neurons by Feiner et al[33]. High concentrations of propofol significantly inhibit NMDA receptor-mediated calcium increase and attenuate Glu neurotoxicity *in vitro*[70,71]. Propofol can inhibit the activation of Glu receptors, the mechanism of which may be attributed to its reducing phosphorylation of ionotropic Glu receptors[72]. Furthermore, Wang et al[21,73] found that the inhibition of AMPA receptor GluR2 subunit internalization may contributed to long-term neuroprotection provided by propofol post-conditioning against focal cerebral I/R injury.

### Propofol and Anti-Apoptosis

Ischemic neuronal injury is characterized by continued neuronal loss for a long time during recovery period, which is called apoptosis, a type of programmed cell death[74,75]. It was shown that propofol used in anesthetic doses protected pyramidal neurons in the hippocampal CA1 subfield against delayed neuronal death normally induced by global brain ischemia[68]. Furthermore, propofol infused at the onset of reperfusion for 30 min significantly attenuated neuron apoptosis in transient middle cerebral artery occlusion (MCAO) rats[17].

The apoptosis regulatory genes B-cell leukemia-2 (Bcl-2) and Bcl-2-associated X protein (Bax) act as anti- and pro-apoptotic regulators respectively. Several studies showed that neuroprotective effects of propofol against neuronal apoptosis after ischemia in rat, which may be related to increase expression of Bcl-2 and decrease expression of Bax[10,76,77]. Another study[78] demonstrates that propofol might attenuate $H_2O_2$-induced PC12 cell apoptosis through the inhibition of signaling pathways mediated by the p38 MAP kinase.

Caspase-3 has been found to play a dominant role in the apoptotic pathway[79]. Zhang et al[80] study showed that propofol attenuated the isoflurane-induced caspase-3 activation in H4-APP cells and mouse brain tissue. But another study[10] indicated that activated caspase-3-dependent apoptotic pathways were not affected by propofol. Glia in CNS contributes to the neuroprotection and survival of neurons, apoptosis of which exists in damaged brains suffering from ischemia and neurodegenerative disease. Acquaviva et al[81] study demonstrates that propofol attenuates peroxynitrite-mediated apoptosis in astroglial cells. Propofol pretreatment also significantly reduced apoptosis in oxygen and glucose deprivation (OGD)/reoxygenation BV2 microglia[82].

Moreover, propofol can markedly attenuate autophagic processes of autophagy (another type of programmed cell death) via the decreased expression of autophagy-related proteins *in vitro* and *in vivo*[83]. Cui et al[84] demonstrated that propofol, at clinically relevant concentrations, attenuated cell death through both autophagic and apoptotic mechanisms in a transient global cerebral I/R model of rat, the effects of which is related to inhibition of p53, a tumor suppressor protein involved in apoptosis.

The neuroprotection of propofol related to inhibition of apoptosis might depend on timing of administration of drugs. The therapeutic window for propofol initiated before the onset of ischemia and lasted until early stage of reperfusion[75].

### Propofol and Anti-inflammation

Glial cells (microglia or astrocytes) play important roles in coordinating the inflammatory brain responses to hypoxia and insult. There are studies showed that propofol suppressed the lipopolysaccharide-induced production of inflammatory substances, including prostaglandin E(2), thromboxane B(2), COX enzyme tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1beta and IL-10, in microglia cells[19,85]. The effect of propofol may be attribute to its regulating toll-like receptors and glycogen synthase kinase-3 expressed in microglia cells, which have been shown to mediate the inflammatory response[82,86-88]. Extracellular adenosine triphosphate (ATP) derived from damaged cells and its receptors in glia participate in the signaling pathways evoked in brain insult. Propofol may modulate glial functions through ATP receptors to exert its anti-inflammatory effect[89,90]. In addition, propofol inhibits the inflammatory reaction by inhibiting the nuclear transcription factor kappa B (NF-kappa B) activation during focal I/R, which may be one of the mechanisms of its neuroprotective function[91] since NF-kappa B is an important transcription factor that plays a key role in oxidative stress and inflammatory responses activated during I/R.

### Propofol and HO-1

As an enzyme, heme oxygenase-1 (HO-1) system can provide substantial cellular protection, which exerts antioxidant, anti-apoptotic and anti-inflammatory effects by cleaving heme into carbon monoxide, biliverdin and free iron[92,93]. The neuroprotective effects of propofol postconditioning in brain I/R injury may be partially through the induction of the HO-1 expression[94]. In another model, propofol increases HO-1 expression dose dependently in primary cultured astroglial cells[53] and mitigates the effects of peroxynitrite-mediated oxidative stress and apoptosis[53,81]. The propofol-mediated HO-1 induction might be signaled through activation of NF-kappa B[53,81]. A better understanding of cytoprotection provided by HO-1 *in vivo* could help us understand the mechanisms involved in its neuroprotective effects of propofol.

### Propofol and Aquaporin 4

Propofol may be involved in neuroprotection by preventing brain edema[18]. Aquaporin 4 (AQP4) plays a key role in maintaining water balance in the CNS, and its dysfunction may lead to brain edema[95]. Treatment with propofol reduces brain edema after transient focal brain I/R[96] or traumatic brain injury[97] in rats, possibly through inhibiting AQP4 over-expression[96,97]. Another study showed that propofol down-regulated AQP4 expression and provided neuroprotective effects in an OGD model of cultured rat astrocytes[98]. The effect of modulating AQP4 expres-

sion of propofol might be associated with attenuated expression of IL-1beta and TNF-alpha and inhibiting NF-kappa B and p38/MAPK pathways by itself[97].

### Propofol and EDTA

Although the physiological significance of neuronal zinc release within the CNS is not clear, and its role in brain injury is controversial[99], it has been proposed that under clinical conditions such as traumatic brain injury, stroke or epilepsy, the excess influx of zinc into neurons has been found to result in neurotoxicity and damage to postsynaptic neurons[100,101]. Propofol formulations contain either EDTA, which has antibacterial and antifungal properties. EDTA is also a chelator of divalent ions such as zinc, magnesium, and calcium. Recently, EDTA has been reported to exert a neuroprotective effect itself by chelating surplus intracerebral zinc in an ischemia model of permanent MCAO[102] and OGD-induced cell damage[102]. Thus, EDTA may be a new contributor to the neuroprotection of propofol.

### Additional Mechanisms

Acute cerebral ischemia is associated with an increased extracellular dopamine accumulation[103]. Wang et al[22] have demonstrated that propofol attenuated dopamine accumulation in the striatum in rat model of temporary MCAO. Moreover, Propofol suppressed the ischemia-induced increase in circulating catecholamines to baseline levels during incomplete cerebral ischemia[61]. Propofol may interfere with $Na^+$ influx through voltage-dependent $Na^+$ channels and inhibit neurotransmitter release[104], including reducing catecholamine secretion in the adrenal medulla and, probably, in the sympathetic nervous system[105]. Attenuation of catecholamine may be one of mechanisms of the neuroprotective property of propofol.

The mitochondrial mechanisms involved in neuroprotective effects of propofol may be related to its preventing the increase in neuronal mitochondrial swelling[14], which is demonstrated in an *in vitro* model of cerebral ischemia by Adembri et al[14]. Uncontrolled opening of the mitochondrial permeability transition pore (mPTP) may lead to mitochondrial swelling during ischaemia-reperfusion injury[106]. It is now considered that propofol-induced closure of the mPTP is the underlying effector mechanism that is responsible for neuroprotection[106]. The data illustrate that propofol mitigated the isoflurane-induced mPTP opening in the H4-APP cells and may ameliorate the isoflurane-induced neurotoxicity by inhibiting its mitochondrial dysfunction[80].

Delayed rectifier potassium current (I(K)) was reported to be closely related to neuronal damage[107]. A study show that propofol inhibited I(K) via the activation of PKC epsilon in rat cerebral parietal cortical neurons[108] and exert its neuroprotective effects.

Transcription factor c-Jun affects neuronal cell death and survival in mammalian brain[109]. There is a study showed that inhibition of c-Jun activity is involved in the neuroprotective effects of propofol on glutamate-induced injury in neuronal PC12 cells[110].

He et al[29] reported that propofol may up-regulate metallothionein-3, a growth inhibitory factor that exhibit neuroprotective effect in the CNS *in vivo*, and play a protective role in hypoxia/reoxygenation model on hippocampal neuron cells *in vitro*.

The cAMP response element-binding protein (CREB) was proposed that its phosphorylation (P-CREB) constituted a convergence point involved in neuroprotection[111]. Propofol could significantly inhibit the decrease of P-CREB level in peri-infarct region, which is involved in high dose propofol-induced neuroprotection of MCAO mice[112].

Ischemic depolarization about the infarction triggers a cascade of biochemical events that play an important role in cerebral injury[113], prolonging the onset or shortening the duration of which may reduces neuronal damage. Kobayash et al's study[60] showed that propofol reduced duration of ischemic depolarization in 2-vessel occlusion model of gerbils.

Basic fibroblast growth factor (bFGF) is a polypeptide with potent trophic and protective effects on the brain and has been reported to exert neuroprotection against a wide variety of insults, including ischemic neuronal injury[114,115]. In a model of MCAO, post-ischemic administration of propofol provides neural protection from cerebral I/R injury. This protection may be related to an early increase in the expression of bFGF[116].

As mentioned above, propofol might regulate various neuroprotection-associated proteins or ion homeostasis to act its neuroprotective effects, which are far from clarification and deserve further exploration.

### Clinical Evidence

Propofol appears to have the same neuroprotective properties with other general anesthetics[117-119], although they have distinct molecular mechanisms

of action. As far as we know, there have been no clinical studies to determine that propofol is more neuroprotective than other general anesthetics in the clinical setting, and even clinical studies showed that propofol may be inferior to other anesthetics. For example, a preliminary study of 20 patients[120] showed that propofol appeared to offer no advantage over isoflurane for cerebral protection during cardiopulmonary bypass. Another randomized controlled trial[121] demonstrated that a sevoflurane-based anaesthesia was associated with better short-term postoperative cognitive performance than propofol. However, propofol, as an intravenous sedative-hypnotic agent, has effects of reducing cerebral blood flow[122,123], cerebral metabolic rate dose-dependently, and intracranial pressure, which is already in use clinically in neurosurgical anaesthesia[124], and now also widely used for the sedation of patients in the intensive care unit. It is difficult to draw conclusions to recommend propofol for clinical use as a neuroprotectant per se, but it might play an important role in the so-called multimodal neuroprotection[36]. Therefore, it will be necessary to further explore the neuroprotective potential of propofol clinically.

## Conclusions

As shown here, accumulating experimental evidence has clearly revealed that the intravenous anaesthetic propofol is an efficacious neuroprotective agent. Although, some studies showed that propofol has no neuroprotective properties and even yielded contradictory results[125-128]. This inconsistency could be due to the types of models, the concentration[126], dose and timing of administration of drugs[129]. The exact mechanisms of propofol's neuroprotection will be required further investigations. More importantly, the investigators working in propofol-related field should pay more attention to the clinical patients of acute cerebral injury, cerebral ischemia, neurosurgical operations, cerebral protection of resuscitation, traumatic brain injury and intracranial space occupying lesions, for whom the research is being conducted.

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

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