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Experimental

Anticonvulsant and Neuronal Protective Effects of Propofol on Experimental Status Epilepticus

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Propofol (2,6-diisopropylphenol) is an intravenous (i.v.) short-acting agent frequently used in neuroanesthesia and recently successfully used to treat refractory status epilepticus (SE). Conversely, there are over 50 reported cases of epileptic seizures following propofol-induced anesthesia, suggesting that propofol may aggravate seizures, especially in seizure-prone patients. The aim of this study is to assess the clinical and histologic effects of propofol on experimental SE. Status epilepticus was induced in adult rats by kainic acid [KA, 20 mg/kg, intraperitoneal (i.p.)]; in this model there is a time interval between KA administration and SE onset. To assess the effects of propofol on seizure-prone rats, propofol was given 15 minutes after the injection of KA before onset of seizures (group I, $N = 12$; 15 mg/kg i.v.). To assess the effects of propofol as an anticonvulsant, it was given 15 minutes after onset of SE to other rats (group II, $N = 8$; 15 mg/kg/i.v.). Control rats were injected with saline in both groups (group I $N = 5$; group II $N = 5$). Histology and immunohistochemistry were used to assess seizure-induced hippocampal cellular damage 2 weeks after SE. In group I rats, seizure latency was not different from controls. Furthermore, SE occurred less frequently in propofol pretreated rats than controls ($p < .05$). In group II rats, propofol broke SE in all treated rats. Furthermore, it reduced SE-induced mortality rate ($p < .05$). Finally, propofol had neuronal protective effects on hippocampal neurons. This resulted in decreased seizure-induced neuronal loss and astrocytosis in propofol-treated animals compared to controls. This study shows that propofol is not proconvulsant. Furthermore, propofol aborts kainate-induced SE and offers protection from seizure-induced hippocampal neuronal damage. **Key Words:** Propofol—Seizures—Hippocampus—Status epilepticus—Neuronal damage—Glial fibrillary acidic protein.

Convulsive status epilepticus (SE) is characterized by seizures lasting more than 30 minutes or consecutive seizures, between which the patient fails to recover consciousness (1). Systemic complications of SE range from hypoxia and lactic acidosis to cardiac arrythmias (2,3). Furthermore, SE can cause cognitive and neurologic deficits, increase susceptibility to chronic seizures, and result in death (4,5). Therefore, recent clinical and experimental research has been focused on developing new drugs for the treatment of refractory SE (6,7).

Recent clinical data suggest that propofol (2,6-

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diisopropylphenol), a fast-acting anesthetic agent, may be successfully used for the treatment of SE (8–12). These data are corroborated by laboratory studies showing that propofol is effectively treating various models of experimentally-induced seizures (13–17). On the other hand, other investigators have shown that propofol has no effects on seizures (18). Furthermore, there is clinical evidence that propofol may have proconvulsant effects in both seizure-prone patients and patients without a history of epilepsy (19–23).

The purpose of this study is to assess the effects of propofol in the treatment of kainic acid (KA)-induced SE in the rat. Seizure severity, latency to seizure onset, mortality, and seizure-induced cellular hippocampal damage were evaluated in order to determine the effectiveness of propofol in the treatment of experimentally induced SE.

Material and Methods

Animals

The experimental procedures were conducted in 30 adult Sprague-Dawley rats (body weight: 250–500 g; Taconic Farms, NY, USA). All animals were maintained on a 12-hour light–dark cycle with an average room temperature of 23°C, humidity of 55%, and food and water ad lib. Experiments were conducted according to our Institutional Animal Care and Use Committee (IACUC) and Center for Laboratory Animal Science (CLAS) guidelines and approved protocols.

Surgery for Insertion of Intravenous Catheter

Rats were anesthetized with chloral hydrate (.3 g/kg; i.p.). Intravenous catheters were placed in the femoral veins of all the animals to allow administration of drugs. After the surgery, the rats were allowed to recover for 24 hours.

Induction of Seizures

Status epilepticus was induced in all animals by i.p. injection of KA (20 mg/kg). In this model, there is a latency between KA administration and onset of seizures. Latency to seizure onset was the time interval between the administration of KA and the first observed clonic seizure. Kainic-acid-induced behavioral seizures consist of clonic movements of one forelimb (mild seizures), bilateral forelimb clonic movements (severe), and tonic seizures leading to SE (24). Status epilepticus was defined as 30 minutes of uninterrupted seizures. After injection of KA, rats were observed for 4 hours and then returned to their cages.

Groups Studied

To assess the effects of propofol as proconvulsant, one group of animals (group I: $N = 12$) was given propofol (15 mg/kg; i.v.) 15 minutes after injection of KA, before onset of seizures. To assess the effects of propofol as an anticonvulsant a second group of rats (group II: $N = 8$) was given propofol (15 mg/kg; i.v.) 15 minutes after onset of SE. In both groups, control rats were injected with saline (group I: $N = 5$; group II: $N = 5$). The sedative effects of propofol were monitored by tail pinch. After i.v. injection of the drug, the rat's tail was gently pinched every minute for 20 minutes. The first motor response to the pinch was recorded as cessation of sedatory effect.

Histology and Immunohistochemistry

The animals were sacrificed 2 weeks after SE. After general anesthesia was delivered, rats were perfused intracardially with .9% NaCl and then 4% paraformaldehyde in 0.1M sodium phosphate buffer (pH 7.4). Subsequently, the brains were removed and embedded in paraffin. Five micron-thick serial sections were stained with hematoxylin and eosin or cresyl violet to assess neuronal morphology and seizure-induced hippocampal neuronal damage. Other sections were immunohistochemically stained for glial fibrillary acidic protein (GFAP; GFAP kit, Dako, Santa Barbara, CA, USA) using standard techniques (25) to assess astrocytosis.

Quantification of Neuronal Damage and GFAP Expression

Five micron-thick sections stained with cresyl violet were used to determine neuronal loss in the hippocampus. In each surviving control and propofol-treated rat of groups I and II, neurons were counted and averaged in two sections of the anterior and posterior ventral hippocampus in each of the following hippocampal subfields: CA1, CA2, and CA3/CA4. Neurons were also counted in an analogous fashion in the same subfields in five control rats not exposed to KA seizures. Cell counts were made at a magnification of 400 × with a custom-made image-analysis system interfaced with a Macintosh computer and IPLab software. (Signal Analytics Corporation, Vienna, VA, USA).

Edge errors were reduced by omitting cells that touched the upper or right side of a square. Neuronal count data are expressed as percentage of persisting neurons in each field in group I and II rats compared to that of rats not exposed to KA. Astrocytic GFAP expression was quantified in the same hippocampal subfields on uncounterstained GFAP stained slides at 400 × magnification counting GFAP positive cells (astrocytes). The number of GFAP-positive astrocytes was compared in control and propofol-treated rats.

Statistical Analysis

Student's unpaired *t*-test was used to compare seizure latency, neuronal counts, and GFAP-positive astrocytes in propofol-treated and control rats. Chi square analysis was used to compare seizure severity and mortality in propofol-treated and control rats. Data are reported as mean ± standard error. A probability of $p < .05$ was considered significant.

Results

In group I rats (pretreatment), the latency to seizure onset in propofol-treated rats was not different from controls. Seizures occurred 65 ± 6 minutes after injection of KA in propofol-treated rats and 78 ± 12 minutes in controls. Furthermore,

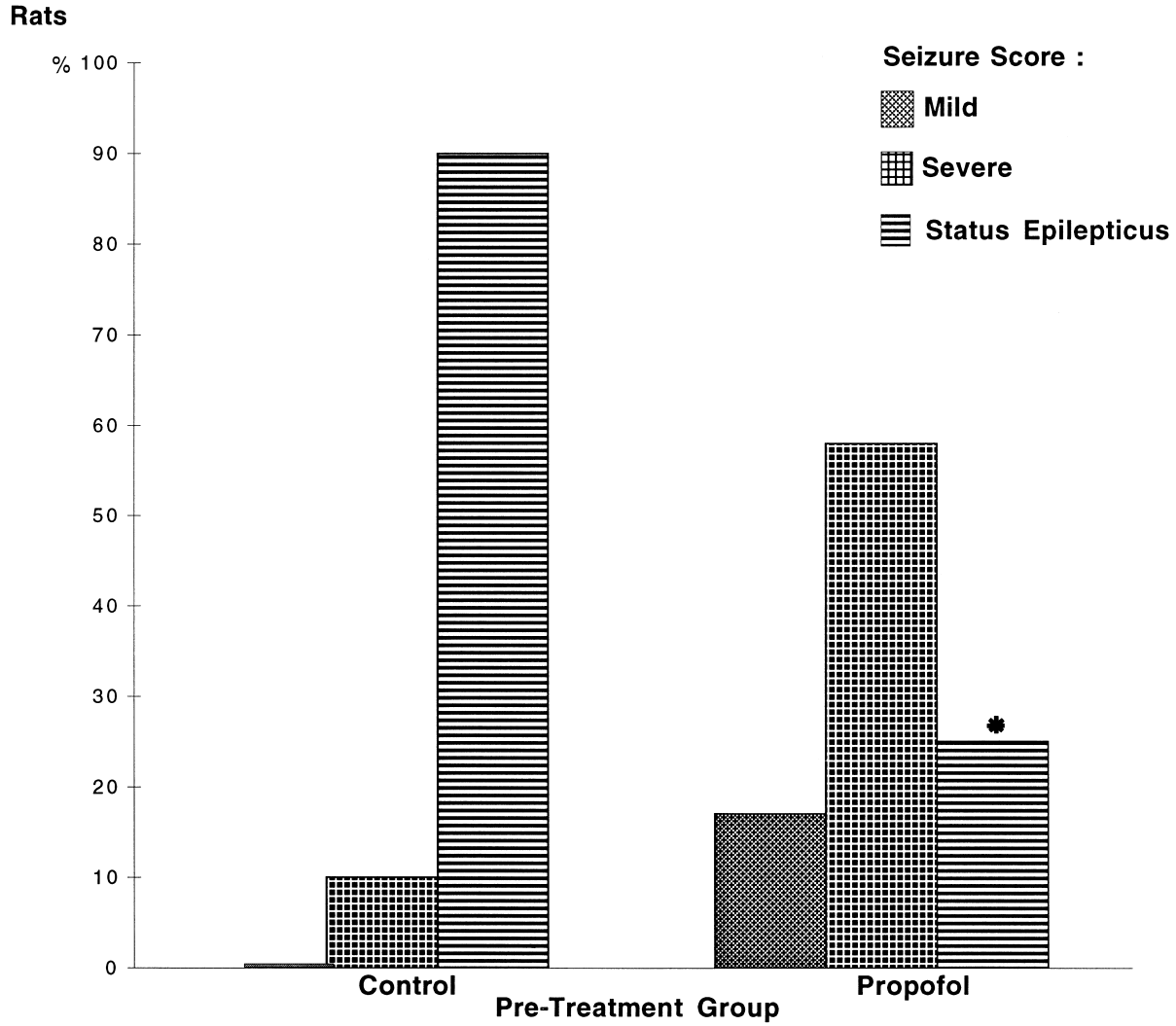

Figure 1. *Propofol did not worsen the severity of seizures in seizure-prone rats (group I). Additionally, propofol pretreated rats had a lower rate of SE. Seizure score: mild = clonic movements of one forelimb; severe = bilateral forelimb clonic movements and tonic seizures; SE = 30 minutes of uninterrupted seizures. Data are expressed as percentage of animals in each group.* *$X^2 = 4.4$; $p = .036$.

seizure severity was not worsened by propofol pretreatment. Additionally, propofol-treated rats had a lower rate of SE than controls: SE occurred in four of five control rats and only three of 12 of experimental animals (Fig. 1).

In group II rats (posttreatment), propofol broke SE in all treated rats (Fig. 2). Furthermore, in both groups, SE-induced mortality was reduced in propofol-treated rats compared to controls (Fig. 3).

The sedative effects of propofol were similar in both groups; propofol induced sedation for 14 ± 2 minutes in group I rats and 16 ± 2 minutes in group II rats.

Histologic examination of rat brain sections 2 weeks after SE showed that seizure-induced neuronal loss in the CA 3/4 hippocampal subfield was significantly less in propofol treated rats than controls (Fig. 4). Additionally, in the same hippocampal subfield, the number of GFAP-positive astrocytes was significantly less in propofol-treated rats than controls [Analysis of variance (ANOVA), Fisher's post-hoc $F(2) = 9.$; $p = .004$]. This is consistent with decreased SE-induced ''glial scar'' in propofol-treated rats (Fig. 4).

Discussion

Medically refractory SE causes irreversible neuronal damage and is potentially life-threatening (3,26,27). Therefore, new drugs are currently sought for its treatment (6,7). Propofol, a hypnotic anesthetic agent, has met wide favor in anesthesia prac-

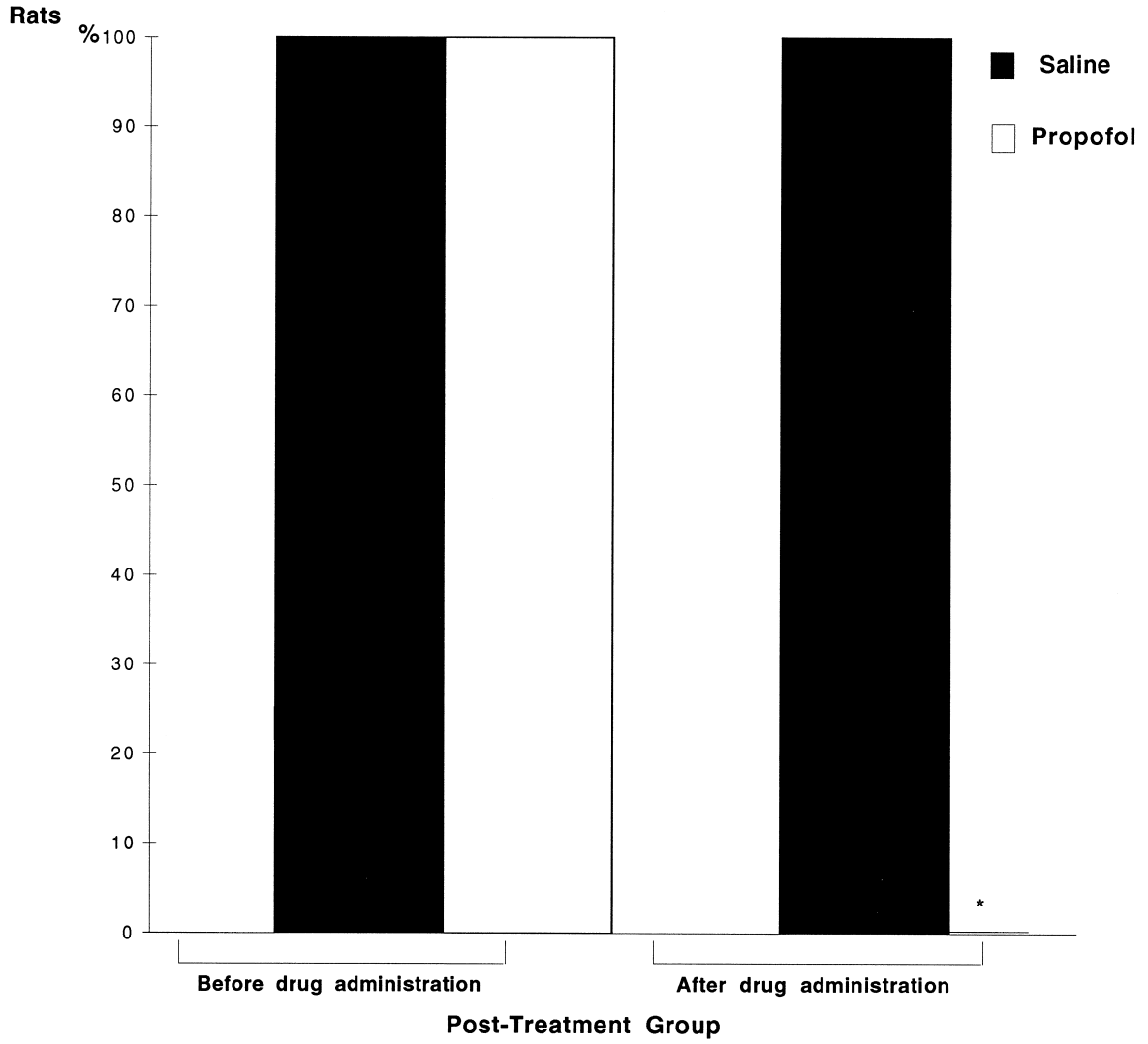

Figure 2. *Propofol broke SE in all treated rats. Data are expressed as percentage of animals with SE in each group.*

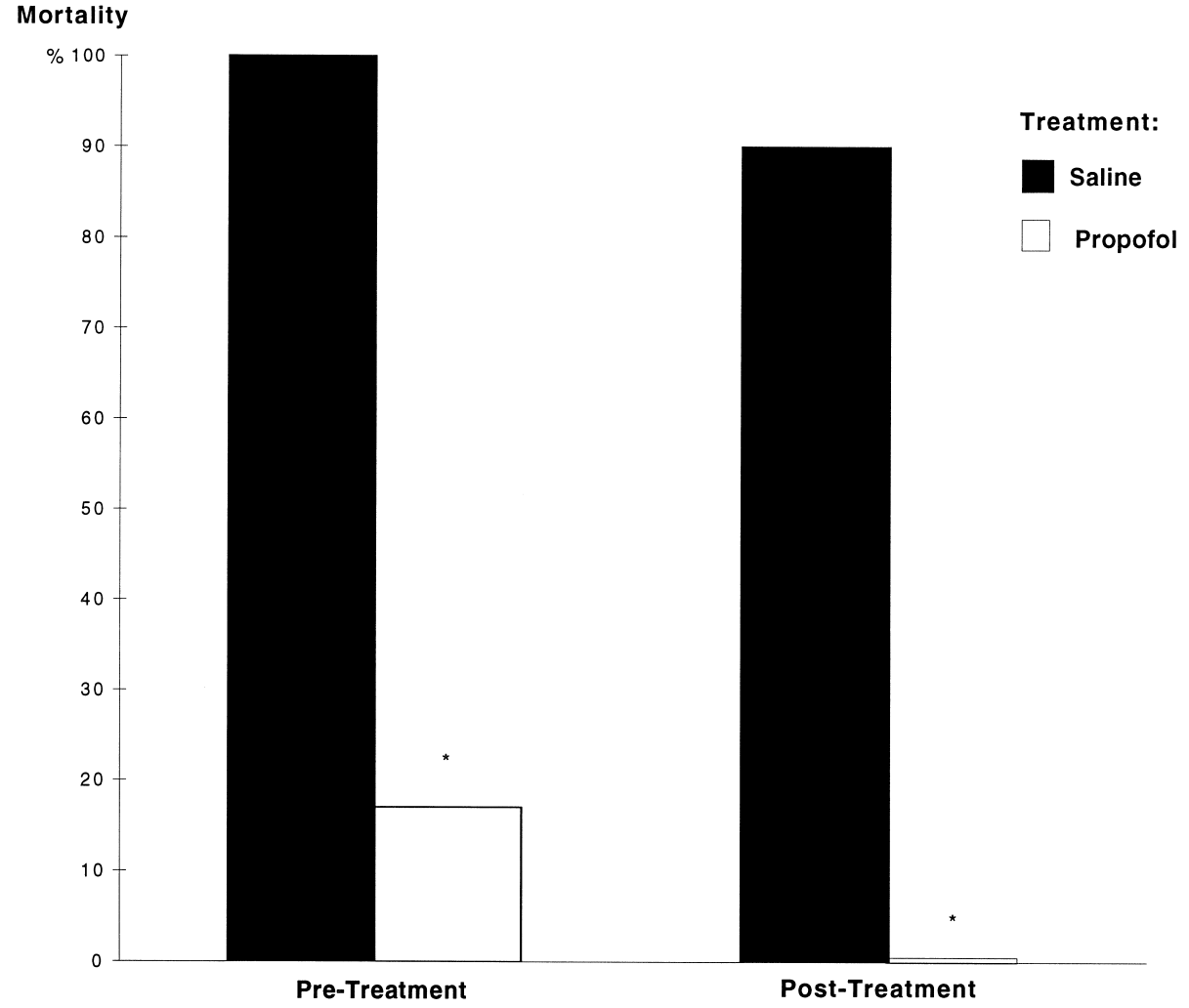

Figure 3. *Propofol-treated rats had a lower mortality rate than controls. Data are expressed as percentage of mortality in each group; pretreatment: propofol,* N = *12; saline,* N = *5; posttreatment: propofol,* N = *8; control,* N = *5. *Chi square analysis, pretreatment* $X^2 = 14.673$; p = *.0001; posttreatment,* $X^2 = 10.811$; p = *.0010.*

tice since its introduction in 1981 (28). Its fast-acting properties including a distribution half-life of 2–4 minutes and quick metabolic clearance of 30–60 minutes, make it particularly desirable, as it allows patients to recover promptly even after prolonged infusion (12,29). Anecdotal data suggest that propofol can be successfully used for treatment of SE (6,9–11). In a recent series of eight adult patients; four with posttraumatic epilepsy and four with no previous history of seizures, SE was safely and efficaciously interrupted (8). Furthermore, propofol has been shown to decrease seizure duration during electroconvulsive therapy in humans (30,31).

Laboratory data support the clinical evidence that propofol has anticonvulsant effects. Propofol was found to be more effective than thiopental in the treatment of experimentally induced convulsions in rats (14,15). Both drugs increased seizure latency, but the effects for propofol were more pronounced, with seizures occurring much later. In the rabbit (16), propofol was shown to have anticonvulsant effects more profound than those of thiopental and similar to those of diazepam. Similar results were found in a mice model (17). In our study we showed that propofol has anticonvulsant effects, as it abated SE in all treated rats. These data corroborate previously reported clinical experience (8–11).

Despite a large body of clinical evidence supporting propofol as an anticonvulsant medication, there are reports suggesting that propofol may have proconvulsant effects. In particular, there is evidence that seizures occurring after anesthesia and opisthotonus can be enhanced by propofol (20–22,32).

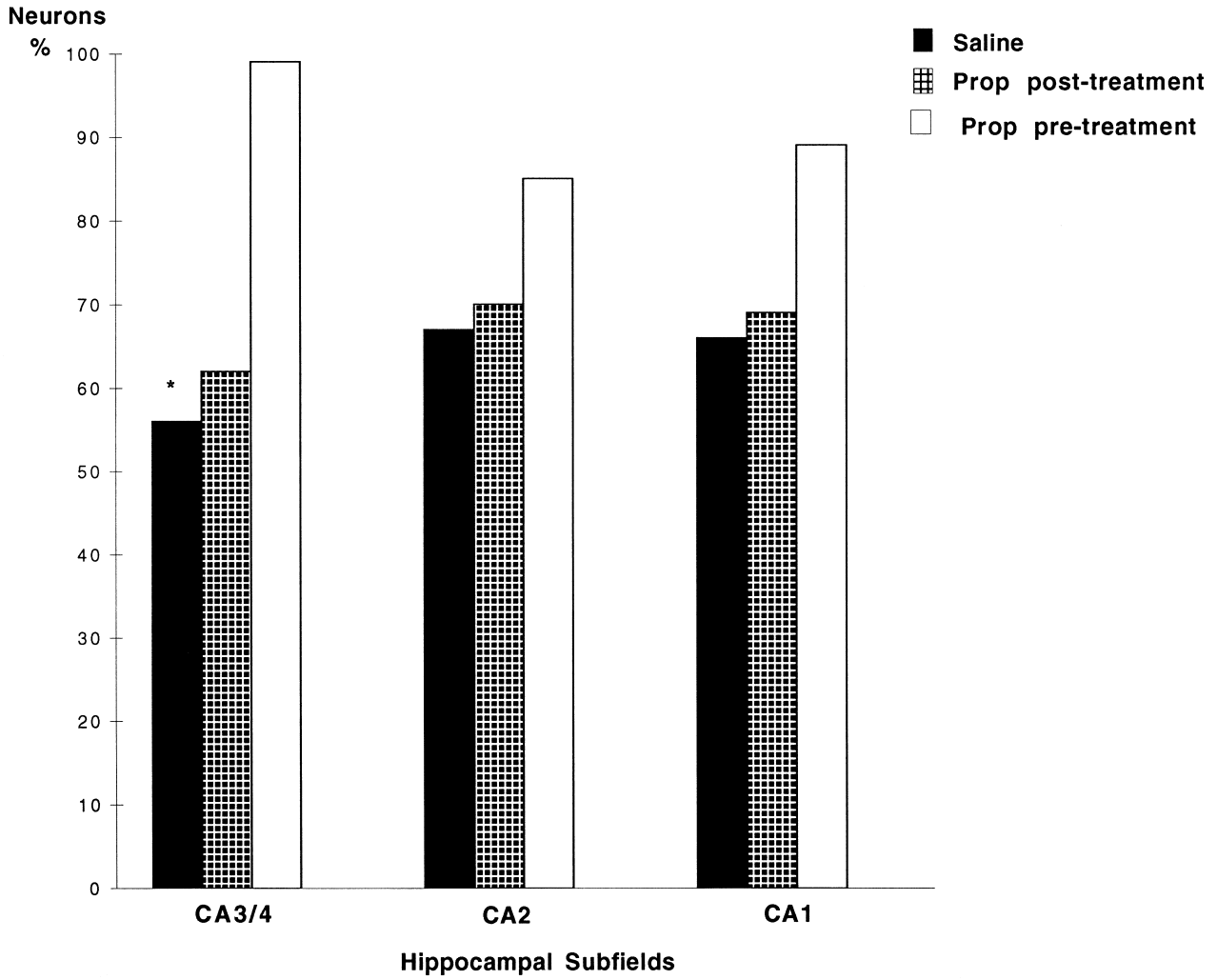

Figure 4. *Propofol treatment resulted in decreased seizure-induced neuronal loss in the CA3/4 hippocampal subfield. Data are expressed as percentage of residual neurons in each subfield compared to untreated rats rats not exposed to seizures (see Material and Methods). *Unpaired Student's* t*-test,* $t(7) = -3.4$; $p = .012$.

The adverse reactions usually occur at the end of general anesthesia (19). Seizures as a result of propofol anesthesia, in patients with and without a previous history of seizures have been reported (23). The incidence of propofol-related seizures is, however, low: 1 in 47,000 administrations (33).

To date the clinical evidence that propofol may have proconvulsant effects has not been corroborated by any experimental study. One laboratory study, however, showed that propofol has no anticonvulsant effects in a mice model (34). To the best of our knowledge, ours is the first study to assess the proconvulsant effects of propofol. We found that rats pretreated with propofol did not have a shorter latency to KA induced seizure onset. Therefore, in this experimental setting, propofol did not have a proconvulsant effect but rather had a demonstrated anticonvulsant effect.

The mechanisms of action of propofol on seizure inhibition are still under investigation. Research shows that propofol could act on several pathways by enhancing γ-aminobutyric acid (GABA)-ergic inhibitory neurotransmission (35,36), depressing Na^+ channels (37), and modulating astrocytic-neuronal connections (38). Enhancement of GABA-ergic inhibitory neurotransmission by propofol is accomplished by activation of the $GABA_A$ receptor-chloride ionophore complex (13). Furthermore, propofol seems to act on NA^+ channels by decreasing their opening time in human brain cortex tissue (37); this in turn will result in neuronal hypoexcitability. Finally, there is evidence that propofol may

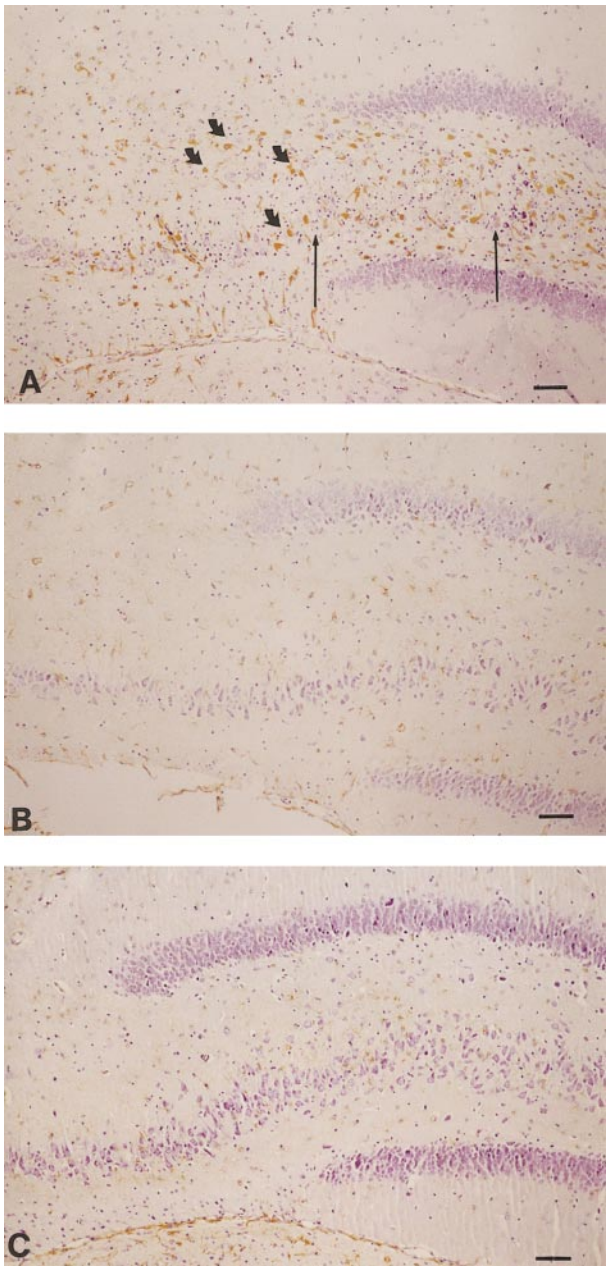

Figure 5. *Photomicrographs of 5 μm coronal rat brain sections at the level of the hippocampus showing GFAP stained sections of (A) saline-treated; (B) propofol pretreated; and (C) propofol posttreated rats. Note the increased presence of GFAP-positive astrocytes in (A) (short arrows on sampled cells). Furthermore, in control rats large areas of neuronal depletion were seen in the CA 3/4 hippocampal subield (long arrows in A). Astrocytic reaction and neuronal loss was less pronounced in propofol treated rats (B and C). Glial fibrillary acidic protein immunohistochemistry stain, cresyl violet counterstain. Bar = 100 μm.*

act on glial cells (38) by decreasing the permeability of gap junction channels between glia and neurons. Further studies, however, are necessary to fully assess the anticonvulsant mechanisms of action of propofol.

The previously mentioned mechanisms of action of propofol may also be in part responsible for neuronal protective effects of propofol on neurons described in experimental studies on cerebral ischemia (39–41). Neuronal damage of ''vulnerable'' pyramidal neurons in the CA1 and CA3/C4 hippocampal subfield after ischemia, hypoglycemia, or seizures is well documented (4,27,42–45). Excitatory neurotransmitters and increased intracellular calcium in the brain are implicated in this excitotoxic effect. The mechanism of action by which propofol may have a protective effect on vulnerable neurons are still unclear. It has been speculated that a key factor in neuronal protection is the decreased cerebral metabolic (CM) rate of O2 caused by propofol (39). However, the protective effects of propofol are not proportional to the CM suppression and various other mechanisms may play a significant role. In particular, Illievich et al. (46) showed that ischemia-induced increased glycine brain concentration is significantly reduced after propofol administration. Glycine is known to potentiate *N*-methyl-D-aspartate (NMDA) response and accelerate neuronal demise (47). Therefore, neurotransmitter-related propofol induced factors may have a role in neuronal protection.

In our study, we show that propofol has protective effects on hippocampal vulnerable neurons after SE. Propofol-treated rats had significantly less seizure-induced neuronal hippocampal loss than controls. Furthermore, propofol reduced the glial reaction that occurs after neuronal demise. Glial proliferation in the temporal lobe is at the basis for mesiotemporal epilepsy (48). Therefore, propofol may have protective effects on the hippocampus preventing formation of a glial scar at the time of SE and, therefore, avoiding future seizures. Further studies targeted to assess this hypothesis are necessary to bring further insights on this issue.

In conclusion, evaluation of current and recent literature provides two contrasting views of the efficacy and safety of propofol use for the treatment of SE. Our study demonstrates that propofol does not exhibit proconvulsant effects in this experimental model. On the contrary, propofol successfully abates SE, decreases SE-induced mortality, and reduces seizure-induced hippocampal neuronal demise. This experimental study corroborates clinical evidence that propofol can be successfully used in treating refractory SE. Furthermore, it is the first study to suggest that propofol may also offers neu-

ronal protection to seizure-induced neuronal damage.

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