

The Effect of Postinjury Administration of Polyethylene Glycol-Conjugated Superoxide Dismutase (Pegorgotein, Dismutec[®]) or Lidocaine on Behavioral Function following Fluid-Percussion Brain Injury in Rats

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ABSTRACT

Previous studies in our laboratory have shown that polyethylene glycol-conjugated superoxide dismutase (PEG-SOD) or lidocaine treatment before experimental fluid-percussion brain injury in rats reduces the cortical hypoperfusion normally found in the early posttraumatic period. The purpose of the current study was to determine if posttreatment with PEG-SOD or lidocaine is also associated with changes in the trauma-induced suppression of motor and cognitive function that occurs following traumatic brain injury (TBI). Twenty-four hours after surgical preparation, rats were randomly assigned to a saline or drug posttreatment group, PEG-SOD (pegorgotein, Dismutec[®], 10,000 IU/kg) or lidocaine (2 mg/kg), which was injected iv 30 min after moderate injury. PEG-SOD completely prevented beam walk latency deficits on days 1–5 postinjury while lidocaine similarly prevented beam walk deficits on days 2 through 5 postinjury. Both drugs produced a statistically insignificant trend for a decrease in beam balance duration deficits on days 1–5 postinjury and had no effect on cognitive function, as assessed by the Morris water maze, on days 11 through 15 postinjury. The mechanism by which PEG-SOD and lidocaine reduce posttraumatic motor deficits may be related to their free radical scavenging effect or previously reported effects on posttraumatic cerebral blood flow. To our knowledge, this is the first report of the effectiveness of these two agents in laboratory animals when administered after traumatic injury.

Key words: brain injury; motor; memory; PEG-SOD; lidocaine; rat; free radicals

INTRODUCTION

ALTERATION OF CEREBRAL BLOOD FLOW following traumatic brain injury may be one component that affects the secondary pathology associated with trauma. Cerebral blood flow studies in rats have shown a persistent cortical flow reduction in the first hour after fluid percussion brain injury (Yamakami and McIntosh, 1991,

1989; Yuan et al., 1988; Muir et al., 1992). In a previous study we examined the effect of pretreatment with a drug of abuse, namely cocaine, on the response to traumatic brain injury. We found that cocaine, and lidocaine, which mimics cocaine's local anesthetic effects, both reduced the cortical hypoperfusion that follows experimental fluid percussion injury in rats (Muir and Ellis, 1992, 1995). Subsequent investigation showed that ad-

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ministration of lidocaine or cocaine before injury also reduced posttraumatic motor deficits (Muir et al., 1995a). Local anesthetics, such as lidocaine, have also been shown to have neuroprotective effects in animal models of ischemia (Rasool et al., 1990) and lidocaine has been reported to have an oxygen radical scavenging action, as well as its well-known local anesthetic action (Das and Misra, 1992).

We have also recently reported that a preinjury bolus followed by a continuous infusion of superoxide dismutase (SOD) dramatically reduces cortical hypoperfusion during the immediate period after traumatic brain injury in rats (Muir et al., 1995b). The supposed effect of SOD would be by scavenging posttraumatically produced oxygen radicals, which have been implicated in the posttraumatic genesis of cerebral endothelial lesions and altered cerebrovascular reactivity (Kontos et al., 1984). While these previous studies of lidocaine's and SOD's effect on trauma provide important information on possible mechanisms that contribute to dysfunction in the period immediately after injury, they do not address the potential efficacy of these agents when given in a manner which would mimic posttraumatic therapy. Since we have had a long-standing interest in these compounds with respect to trauma and both have been found to increase posttraumatic brain perfusion and scavenge oxygen radicals we examined both these compounds in a single, more efficient study. Thus the goal of this study was to determine the effect of PEG-SOD and lidocaine on behavioral dysfunction when given after trauma.

METHODS

Surgical Preparation and Experimental Design

All experimental protocols were approved by our Institutional Animal Care and Use Committee. Two major experiments were conducted. In the first, sham ($n = 8$), saline ($n = 11$) and PEG-SOD ($n = 9$, Dismutec®, 10,000 IU/kg, Sanofi Winthrop, Collegeville, PA) groups were examined. In the second experiment, saline ($n = 10$) and lidocaine ($n = 12$, 2 mg/kg iv) groups were compared to the above-mentioned sham group. The 2 mg/kg lidocaine dose was chosen because it caused improved cortical blood flow and behavioral function in our previous studies where lidocaine was given before injury (Muir and Ellis, 1995; Muir et al., 1995a). The 10,000 IU/kg dose of PEG-SOD was chosen because it is one of the postinjury administration doses that has produced a desirable outcome in humans with traumatic brain injuries in a phase II trial (Muizelaar et al., 1993).

As previously reported (Muir et al., 1995a), rats were surgically prepared for injury under sodium pentobarbi-

tal anesthesia (54 mg/kg) 24 h before fluid percussion or sham injury. Animals were placed in a stereotaxic frame and the scalp sagittally incised. A 4.8-mm-diameter hole was trephined into the skull over the sagittal suture midway between bregma and lambda. Two skull screws (2–56 × 6 mm) were placed in burr holes 1 mm rostral to bregma and 1 mm caudal to lambda. A modified Luer-Loc syringe hub with a 2.6 mm inside diameter was placed over the exposed, intact dura mater and bonded in place with cyanoacrylate adhesive and dental acrylic. After the acrylic hardened, the injury tube was plugged with Gelfoam®, and the scalp sutured closed over the injury tube. Bacitracin was applied to the wound and the animal returned to its home cage.

The next day, rats were randomly assigned to sham, saline, or drug posttreatment groups. Approximately 4 min prior to injury, the rats were anesthetized with 4% isoflurane in 75% N₂O, 30% O₂. Animals were removed from anesthesia, attached to the fluid percussion device, and injured at the threshold of a surgical plane of anesthesia, as determined by toe pinch reflex. This was done to ensure that all animals were injured at the same depth of anesthesia. The rats received a fluid percussion injury of a moderate intensity, being 2.0–2.2 atmospheres in pressure. This injury magnitude is not associated with neuronal cell death, axonal injury, or ischemia (Chou et al., 1991; DeWitt et al., 1988; Lyeth et al., 1990) and has been shown to produce transient neurological signs of areflexia, unconsciousness, and stupor similar to that observed in other species and humans (Dixon et al., 1987; Lyeth et al., 1988a). This level of injury is, however, associated with motor and cognitive deficits (Dixon et al., 1987; Lyeth et al., 1990; Hamm et al., 1993). Saline, lidocaine, or PEG-SOD was administered iv 30 min after injury. The rationale for the 30 min postinjury administration was that 30 min is likely the soonest after injury that an approved agent might be given for human traumatic injury. However it should be realized that the time course of posttraumatic biochemical and other events, as well as the therapeutic window, is likely different in humans, as compared to rats. Beam walking and beam balance motor function were assessed on days 1–5 postinjury. Cognitive function was assessed using the Morris water maze on postinjury days 11–15.

Description of Experimental Methods

The fluid percussion device used to produce experimental brain injury has been described elsewhere (Dixon et al., 1987; McIntosh et al., 1989). Briefly, the device consists of a saline-filled cylinder 60 cm long and 4.5 cm in diameter, which has a movable piston on one end. The opposite end of the cylinder has a pressure transducer housing that terminates with a tube that fits inside the

plastic hub over the exposed dura of the right parietal cortex. Injury is induced by dropping a weighted pendulum that strikes the piston, thus producing a transient pressure pulse. This results in the injection of a small volume of saline into the closed cranial cavity and causes a transient (approximately 20 msec) displacement and deformation of the brain and neural tissue throughout the cranial vault. The magnitude of injury is controlled by varying the height from which the pendulum is released. The duration and intensity of the fluid percussion pressure pulse are recorded on a storage oscilloscope.

Gross vestibular motor function was evaluated with a beam balance task (Dixon et al., 1987). The beam balance task involves placing the rats on a suspended narrow (1.5-cm-wide) wooden beam and measuring the duration they remained on the beam (the maximum limit was 60 sec). Rats were trained on the beam balance 24 h before surgery. Preinjury baselines were established 1–2 h before injury or sham injury. Rats had to balance on the beam for 60 sec on three consecutive trials to meet both training and preinjury baseline criteria. During postinjury behavioral assessment, the animals were placed on the beam three times and the mean latency of the three trials was used for each daily session. Beam balance performance was measured for 5 days after injury.

Fine motor coordination was assessed with the beam-walking task (Dixon et al., 1987). Rats were trained to escape a bright light and loud noise by traversing an elevated 100-cm-long, 1.5-cm wide, wooden beam to enter a darkened goal box at the opposite end of the beam. Four steel pegs (3 mm diameter, 4 cm high) were placed alternately and at equal distances along the inside and outside edges of the beam. Animals were trained on this task 24 h before surgery. One to two hours before injury or sham injury, baseline measures for beam walking were established. Rats were required to successfully complete the task in less than 5 sec for each of three consecutive trials. During testing, animals were placed at the end of the beam close to the light and noise source. The light and noise were terminated when the rat entered the goal box at the opposite end of the beam. After entering the goal box, the animal was allowed to remain for 30 sec. Performance was assessed by recording the latency of the animals to enter the goal box. The data for each daily session consisted of the mean of three trials. Animals were assessed on the beam walking task for 5 days after injury.

Cognitive function of brain-injured animals was assessed using the Morris water maze. The Morris water maze procedure (Morris, 1981) employs a 180-cm-diameter, 60-cm-high metal pool painted black and filled with water to a depth of 27 cm. Water temperature was maintained at $25 \pm 2^\circ\text{C}$ throughout the duration of wa-

ter maze testing. A Plexiglas platform 10 cm in diameter and 25 cm high (i.e., 2 cm below the water surface) was used as a hidden goal platform. The pool was located in a 2.5×2.5 -m room with numerous extramaze cues (e.g., windows, pipes, bookcase) that remained constant throughout the experiment.

The water maze procedure consisted of 4 trials per day for 5 consecutive days (days 11–15 after injury). Delayed testing in the water maze allowed ample time for deficits in motor performance to recover so as not to confound the interpretation of cognitive function. On each trial, rats were placed in the pool by hand and facing the wall, at one of four start locations (south, west, north, and east). Rats started a trial once from each of the four possible start locations on each day. The order of starting locations was randomized for each animal on each day. The goal platform was positioned 45 cm from the outside wall of the pool and was placed in the southeast quadrant of the maze for all groups. Rats were given a maximum of 120 sec to find the hidden platform. If the rat failed to find the platform after 120 sec it was placed on the platform by the experimenter. All rats were allowed to remain on the platform for 30 sec before being placed in a heated incubator (30°C) between trials. There was a 4-min intertrial interval. Previous research has demonstrated that the Morris water maze, as it was employed in these experiments, is unlikely to be confounded by visual, motor or other noncognitive factors (Hamm et al., 1994) and is sensitive to pharmacological interventions (Hamm et al., 1993). Behavioral evaluators were blind to the pharmacological treatment group of all animals.

Statistical Analysis

Each outcome measure was analyzed separately by a split-plot analysis of variance (Group \times Day). If a significant group effect or interaction was found, individual ANOVAs were calculated comparing groups over days. Statistical significance was considered to be $p \leq 0.05$.

RESULTS

Injury Intensity and Body Weight

The mean intensity of injury in the animals used for the PEG-SOD experiments was 2.17 ± 0.2 ($\bar{x} \pm \text{SEM}$) atmospheres. Injury intensity was slightly lower in the lidocaine experiments and averaged 2.06 ± 0.02 atmospheres. The mean body weights ($\pm \text{SEM}$) for each of the various groups prior to injury and for 5 days after injury are presented in Figure 1. The ANOVAs indicated that both the injured animals treated with PEG-SOD, lidocaine, or saline had significantly lower body weights than

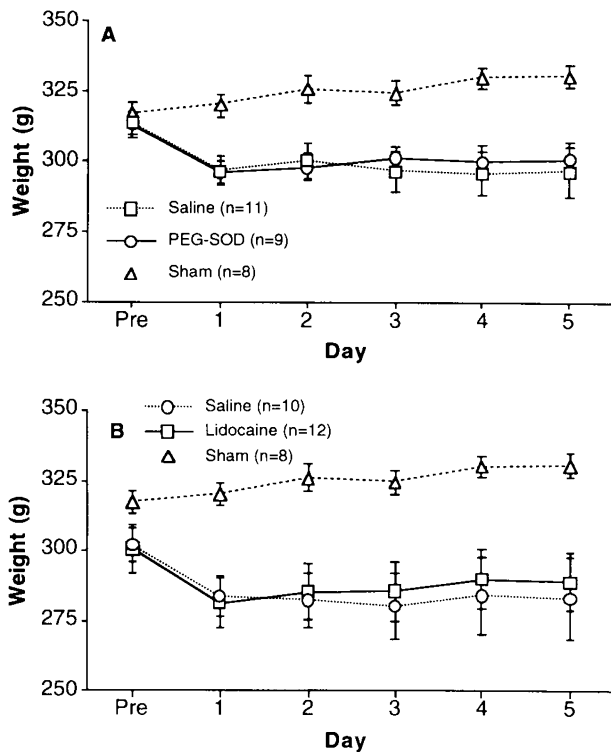


FIG. 1. The effect of PEG-SOD (A) and lidocaine (B) on body weight loss after injury. Neither drug reduced body weight losses that are normally associated with fluid percussion brain injury. For purposes of clarity the same single sham group ($n = 8$) is presented in both figures.

sham injured animals ($p < 0.05$, for each group comparison). Thus, neither PEG-SOD nor lidocaine reduced the trauma-induced weight loss.

Beam-Balance Duration

The mean beam-balance durations (\pm SEM) prior to injury and for the first 5 days after injury are illustrated in Figure 2. The ANOVAs indicated that the injured animals treated with saline exhibited shorter beam-balance durations than the sham-injured animals ($p < 0.05$). Although the injured animals treated with PEG-SOD had longer average beam-balance durations than the injured animals treated with saline (see Fig. 2A), this difference did not reach statistical significance ($p < 0.25$). However, the injured animals treated with PEG-SOD were not different from sham-injured animals. In Figure 2B, the ANOVA comparing the saline-treated injured group to that of the sham-injured group indicated that the injured saline-treated animals had a significantly shorter balance duration than the sham-injured animals on the first day after injury ($p < 0.05$). Also shown in Figure

2B, animals treated with lidocaine had, on the average, shorter beam-balance durations, but again there was no statistically significant difference between saline- and lidocaine-treated animals ($p < 0.15$). As was the case with PEG-SOD treatment, lidocaine-treated animals were not different from sham-injured rats. Therefore, PEG-SOD and lidocaine both displayed similar trends for reduction in beam-balance deficits, which did not reach statistical significance when compared to saline-treated animals.

Beam-Walking Latency

The beam-walking latency (\pm SEM) prior to injury and for the first 5 days after injury is shown in Figure 3. The injured animals treated with saline exhibited longer beam-balance latencies than the sham-injured animals ($p < 0.05$). PEG-SOD treatment reduced beam-walking deficits compared to injured vehicle-treated animals ($p < 0.05$). Analysis of the data for the animals treated with PEG-SOD indicated that beam-walking latency was not different from sham control animals on days 1–5 postinjury. An ANOVA of the data illustrated in Figure 3B re-

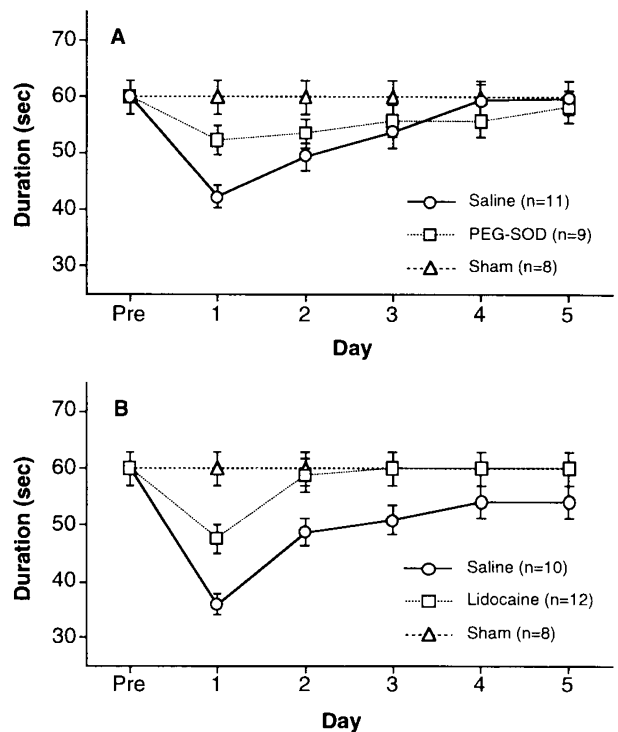


FIG. 2. The effect of PEG-SOD (A) and lidocaine (B) on beam balance duration. Although PEG-SOD and lidocaine treatment appeared to reduce beam-balance deficits compared to injured vehicle-treated animals, the effects were not statistically significant. For purposes of clarity the same single sham group ($n = 8$) is presented in both figures.

PEG-SOD/LIDOCAINE AND BRAIN INJURY

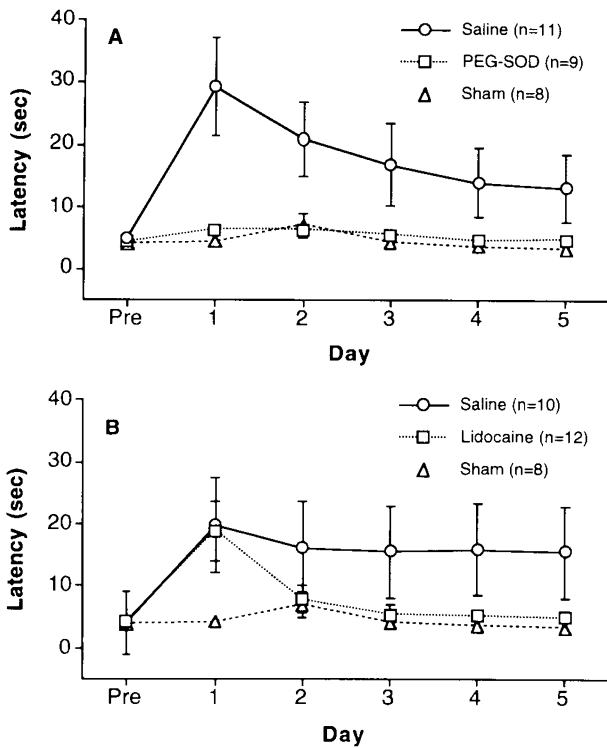


FIG. 3. The effect of PEG-SOD and lidocaine on beam walking latency. For purposes of clarity the same single sham group ($n = 8$) is presented in both figures. (A) PEG-SOD treatment reduced beam-walking deficits compared to injured vehicle-treated animals ($p < 0.05$). As the figure illustrates, the injured animals treated with PEG-SOD performed as well as sham injured animals. (B) Lidocaine treatment reduced beam-walking deficits compared to injured vehicle-treated animals ($p < 0.05$). On days 2–5 after injury, the animals treated with lidocaine performed as well as sham-injured animals.

vealed that the injured saline-treated animal's beam-walking latencies were not significantly different from sham-injured animals's latencies ($p < 0.15$). Lidocaine treatment reduced beam-walking deficits compared to injured vehicle-treated animals ($p < 0.05$). Similarly, in the lidocaine-treated group, beam-walking latency was not different from sham-injured controls on days 2–5 postinjury. Therefore, both lidocaine and PEG-SOD reduced motor deficits normally seen after traumatic brain injury.

Morris Water Maze

The mean latency (\pm SEM) to reach the goal platform during maze testing on days 11–15 is presented in Figure 4. An ANOVA of the data represented in Figure 4A indicated that injured animals treated with saline took longer to find the goal platform than sham-injured animals ($p < 0.002$). Although the injured animals treated

with PEG-SOD found the platform on average faster than the injured animals treated with saline, this difference was not statistically significant ($p < 0.20$). In Figure 4B, animals treated with lidocaine also performed more poorly than sham animals in the Morris water maze ($p < 0.05$). However, in the study in which lidocaine's effect was tested, it should be noted that the saline-treated injured animals on days 11–15 did not have as great a deficit as the saline-treated animals in the PEG-SOD experiment. This is witnessed by the fact that the goal latency for the saline-treated group was only approximately 75 sec in the lidocaine group whereas the goal latency in the saline-treated animals for the PEG-SOD group was 100 sec on the first day of maze testing. Therefore, on the whole, both saline and drug-treated animals in the lidocaine study showed less deficits with respect to their capacity to find the platform in the Morris water maze. We are uncertain as to why the goal latency was not more similar for the saline groups in the PEG-SOD and the lidocaine studies. The atmospheres pressure injury was slightly lower in the lidocaine study saline group (see

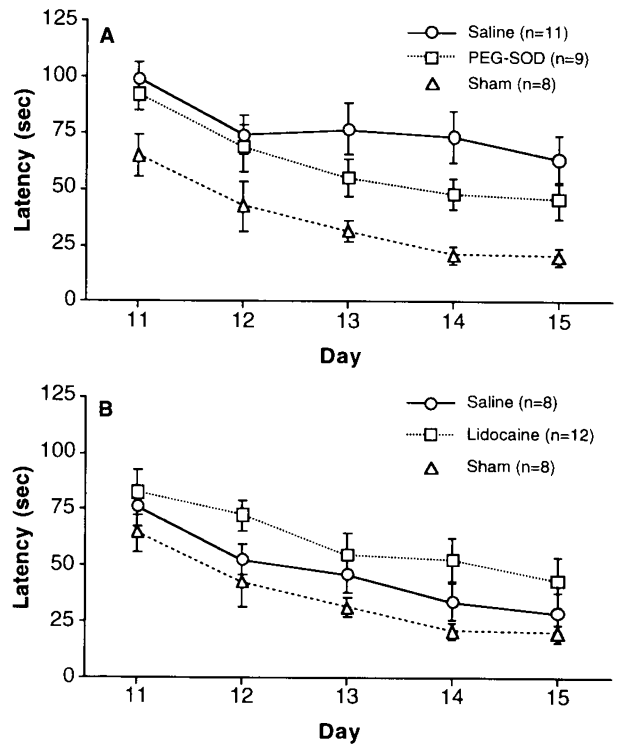


FIG. 4. The effect of PEG-SOD (A) and lidocaine (B) on performance in the Morris water maze. Neither lidocaine or PEG-SOD treatment affected Morris water maze performance. For purposes of clarity the same single sham group ($n = 8$) is presented in both figures.

above), however this may not be the reason for the discrepancy between the two groups.

DISCUSSION

The current study has examined how posttrauma administration of lidocaine, an agent known primarily for its local anesthetic properties, and PEG-SOD, an agent known for its capacity to scavenge superoxide anions, affects behavioral deficits following trauma. It should be noted that in addition to its local anesthetic properties lidocaine has also been reported to be a hydroxyl radical scavenger (Das and Misra, 1992). Thus both drugs may be working via oxygen radical scavenging. Both agents profoundly reduced the fine motor deficits that are assessed by beam walking latency. In fact, these two agents virtually eliminated these deficits. Both agents also caused a strong trend for reduction in beam balancing deficits, although neither effect reached statistical significance at the $p \leq 0.05$ level. And, again similarly, both agents failed to reduce cognitive learning deficits measured by the Morris water maze procedure.

Our results with PEG-SOD are particularly significant since numerous studies have implicated oxygen free radicals in the sequelae of experimental traumatic injury and especially in the cerebrovascular consequences of trauma. Free radical scavengers such as superoxide dismutase and catalase have been shown to prevent the endothelial lesions, sustained arteriolar dilation, and altered vascular reactivity that normally occur after experimental traumatic brain injury (Wei et al., 1981). We have also very recently shown that infusion of SOD nearly eliminates cortical flow deficits that occur immediately following traumatic brain injury in rats (Muir et al., 1995b). Several *in vivo* studies have suggested the site of beneficial action of SOD in the injured brain is the vasculature. Our recent studies of traumatically injured endothelial cells in culture support the endothelial cell as a generator of oxygen radicals and as a target for superoxide dismutase efficacy in reducing endothelial cell injury (McKinney et al., 1996). Importantly, PEG-SOD has been shown to reduce dead plus vegetative outcomes in a phase II clinical trial in traumatically brain-injured humans (Muizelaar et al., 1993). While this plethora of work has supported the efficacy of SOD, it is surprising that no previous studies have examined the effect of SOD on behavioral outcome after experimental brain injury.

Release of the neurotransmitters glutamate and acetylcholine following traumatic brain injury has been implicated in contributing to TBI pathophysiology (Faden et al., 1989; Gorman et al., 1989). This nonspecific neurotransmitter release is thought to be due to membrane de-

polarization that occurs upon impact (Katayama et al., 1990). Antagonists at muscarinic and glutamatergic sites reduce posttraumatic motor dysfunction (Hayes et al., 1988; Faden et al., 1989; Lyeth et al., 1988a,b). Lidocaine causes a use-dependent block of sodium channels (Butterworth and Strichartz, 1990), and this may decrease injury-induced depolarization, thus leading to membrane stabilization and decreased neurotransmitter release. This may be one mechanism by which lidocaine reduces traumatically induced motor function deficits following brain injury. However, it should be noted that lidocaine was not administered until 30 min after TBI, and by this period the majority of the nonspecific release of neurotransmitters that occurs after trauma may have already produced its effect.

One complicating issue with respect to attributing the behavioral effects of lidocaine and PEG-SOD to effects of blood flow is the known time course of blood flow deficits in traumatically injured rats. In the current studies lidocaine and PEG-SOD were not given until 30 min after injury, and it has been reported by some investigators that cerebral blood flow in rats is back to normal by 2 h postinjury (Yamakami and McIntosh, 1991, 1989). However, whether secondary, later-occurring deficits in blood flow occur following trauma in rats is uncertain. If any such later-occurring events do happen, PEG-SOD will still likely be efficacious because of its long, 40-plus-h half-life. However lidocaine's half-life is much shorter, on the order of 2 h in humans.

Pretreatment with lidocaine or PEG-SOD did not improve cognitive function on days 11–15 postinjury as compared to the saline-pretreated animals. However, the preinjury administration of antagonists at glutamatergic and muscarinic cholinergic sites has been shown to improve posttraumatic cognitive function in rats (Hamm et al., 1993). Differences between drug influence upon motor and cognitive function reported in this study may result from differential blood flow changes that occur in the cortex and hippocampus following injury. Fluid percussion TBI is known to cause significant reduction in cortical blood flow but only minimal reductions in hippocampal blood flow in rats (Muir et al., 1992; Yamakami and McIntosh, 1991). It is possible that elevation in posttraumatic cortical blood flow by lidocaine and PEG-SOD may have contributed to reduced motor dysfunction. Compromise of hippocampal blood flow may not be a mechanism of posttraumatic cognitive dysfunction, since hippocampal-mediated memory deficits occur in the absence of significant reductions in hippocampal blood flow. Thus, improvements in blood flow by lidocaine and PEG-SOD, while possibly contributing to improved motor function, may not render any benefit to learning and memory in this model.

In summary, this is the first study to show that post-traumatic administration of PEG-SOD or lidocaine reduces motor deficits after experimental traumatic brain injury. Our results support the continued testing of free radical scavengers for treatment of trauma and support previous investigations, indicating the efficacy of the local anesthetic lidocaine for the treatment of ischemic brain injury.

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