JOURNAL OF NEUROTRAUMA
Volume 10, Number 4, 1993
Mary Ann Liebert, Inc., Publishers

Beneficial Effect of the Nonselective Opiate Antagonist Naloxone Hydrochloride and the Thyrotropin-Releasing Hormone (TRH) Analog YM-14673 on Long-Term Neurobehavioral Outcome following Experimental Brain Injury in the Rat

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ABSTRACT

Neurobehavioral dysfunction following traumatic brain injury results, in part, from delayed biochemical changes initiated by the traumatic insult. Endogenous opioid peptides have been implicated as one type of neurochemical factor involved in the delayed pathological sequelae of central nervous system (CNS) injury, including brain trauma. Both opiate antagonists and thyrotropin-releasing hormone (TRH) and its analogs, which antagonize the physiologic effects of endogenous opioids, have been shown to improve cardiovascular, cerebrovascular, metabolic, and neurologic status following both traumatic and ischemic CNS injury. The present study evaluated the ability of the opiate antagonist naloxone hydrochloride to improve posttraumatic neurologic motor function following experimental fluid-percussion brain injury in the rat, and compared the therapeutic effectiveness of naloxone to the long-acting, centrally active TRH analog YM-14673. Thirty minutes following fluid-percussion brain injury of moderate severity, animals received an intravenous bolus of either naloxone (2.0 mg/kg with constant infusion of 1.7 mg/kg/h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline ($n = 8$). Although naloxone caused a modest and nonsignificant increase in mean arterial blood pressure (MAP), YM-14673 significantly increased MAP within 5 min of administration ($p < 0.05$), an effect that continued up to 4 h postinjury. Postinjury administration of both naloxone and YM-14673 caused a significant improvement in neurobehavioral outcome which persisted up to 4 weeks postinjury. These results suggest that endogenous opioid peptides may

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be involved in the pathologic response to traumatic CNS injury and that pharmacotherapies directed at antagonizing opioid peptides may enhance neurobehavioral recovery after brain injury.

INTRODUCTION

Endogenous opioid peptides have been proposed as one of the delayed neurochemical factors that may play a role in the pathophysiological sequelae of central nervous system (CNS) injury. These endogenous neurotransmitters have been shown to be released following spinal cord injury and appear to contribute to the pathophysiology of spinal injury through actions on microcirculatory blood flow (Faden et al., 1981; Flamm et al., 1982; Holaday and Faden, 1980; Young et al., 1981), or via an interaction with the excitatory amino acid neurotransmitters (EAA) glutamate and aspartate (Bakshi et al., 1990; Bakshi and Faden, 1990; Caudle and Isaac, 1988; Isaac et al., 1990; Faden, 1992). Over the past decade, experimental evidence has accumulated suggesting that endogenous opioid peptides may play a role in the pathogenesis of many other forms of CNS injury, including cerebral ischemia and traumatic brain injury (TBI).

Recent experimental evidence suggests that the κ-opioid receptor ligand dynorphin is the predominant pathologic opioid peptide in traumatic spinal cord injury (Faden et al., 1984; Faden, 1990; Long et al., 1987, 1988; Przewlocki et al., 1983). Tissue concentrations of dynorphin increase, in a dose-related manner, at the injury site with increasing degrees of traumatic spinal injury (Faden et al., 1984). Similarly, a significant increase in regional immunoreactive dynorphin has been reported at 2 h following experimental fluid-percussion traumatic brain injury (McIntosh et al., 1987b). No significant alterations were observed in leucine-enkephalin immunoreactivity in this study, while b-endorphin was found to decrease in the hypothalamus only after severe brain injury. In a subsequent study, regional increases in dynorphin immunoreactivity were found to correlate significantly with local histopathologic damage and reductions in regional cerebral blood flow (rCBF) (McIntosh et al., 1987a). We have therefore proposed that, like spinal cord injury, the activation or release of the endogenous opioid dynorphin and κ-opiate receptor systems, may play a role in the injury process following brain trauma. These hypotheses have provided the rationale for the evaluation of opioid receptor antagonists in the treatment of traumatic brain injury.

Based upon the original studies demonstrating that administration of high doses (2–10 mg/kg) of the nonselective opiate antagonist naloxone could reverse the neurologic deficit and improve regional spinal cord blood flow changes associated with spinal trauma, Hayes and co-workers (1983) were the first to demonstrate that administration of naloxone (10 mg/kg) significantly reversed the hypotension and reduction in pulse pressure, improved blood gas and electroencephalographic (EEG) parameters, and significantly improved brain perfusion after experimental fluid-percussion brain injury in the cat. More recently, we have reported that the opiate antagonist Win 44,441-3, which has enhanced activity at κ-opioid receptor sites, significantly improved cardiovascular function, EEG amplitude, and reductions in rCBF in a stereospecific manner following fluid-percussion brain injury in the cat (McIntosh et al., 1987a). Using nuclear magnetic resonance spectroscopy (MRS), we have also shown that the opiate antagonist nalmefene (which also has enhanced activity at κ-receptors) can improve cellular bioenergetic status and neurologic outcome and restore intracellular free magnesium homeostasis following fluid-percussion brain injury in the rat (Vink et al., 1990). A subsequent study has likewise reported the therapeutic efficacy of the selective κ-opioid antagonist nor-binaltorphimine in the treatment of brain trauma in the rat (Vink et al., 1991). However, the role of specific endogenous opioid systems in CNS injury may be more complicated than previously thought. For example, pretreatment at 15 min with low doses of naloxone (0.1 or 1.0 mg/kg), which putatively block μ-opiate receptors, significantly exacerbated neurologic deficits associated with traumatic brain injury (Hayes et al., 1990), suggesting that some classes of endogenous opioids (μ agonists) may protect against, while others (κ agonists) may exacerbate long-term neurologic deficits produced by brain injury.

The ability of thyrotrophin-releasing hormone (TRH) to physiologically antagonize many effects of the endogenous opioid peptides without altering their analgesic properties (Holaday et al., 1978) has provided the

impetus for the examination of this endogenous factor in the treatment of conditions known to benefit from opiate receptor antagonist treatment. TRH was first reported to be effective in improving concussive-like disturbances caused by head impact in awake mice (Manaka and Sano, 1978) and neurologic dysfunction following compressive brain injury in the cat (Fukuda et al., 1979). We have previously reported that administration of a long-acting, centrally active TRH analog, CG-3703 at 30 min following fluid-percussion brain injury in rats can improve systemic blood pressure, neurologic function, and survival (McIntosh et al., 1988b). Administration of CG-3703 also induces a significant recovery of the intracellular phosphocreatine/inorganic phosphate ratio (PCr/P_i) (McIntosh et al., 1988b) and intracellular free magnesium concentrations (Vink et al., 1988), measured using phosphorus MRS, which suggests that TRH analogs may have direct effects on cerebral metabolism and ion homeostasis when administered to block opiate receptors after brain injury. Faden (1989) has also reported that the TRH analog YM-14673 improves neurologic function after both traumatic brain and spinal cord injury in rats. The present study compared the long-term effects of post-injury administration of high dose naloxone and YM-14673 on cardiovascular and neurologic function following parasaggital fluid-percussion brain injury in the rat.

METHODS

Surgical Preparation

In the present study, we adhered to the animal welfare guidelines set forth in the National Institutes of Health "Guide for the Care and Use of Laboratory Animals," Publication No. 85-23, 1985. Male Sprague–Dawley rats ($n = 24$) were anesthetized with intraperitoneal administration of sodium pentobarbital (60 mg/kg). Sodium pentobarbital was chosen as the anesthetic agent since all previous pharmacologic, behavioral, and neurochemical studies in our laboratory with this model of brain injury have been performed under pentobarbital anesthesia. Each anesthetized rat was placed in a stereotaxic frame and the scalp and temporal muscle were reflected. A 2.0-mm hollow female Leur-Lok fitting was rigidly fixed with dental cement to the animal's skull over a craniotomy centered above the left parietal cortex, 5 mm anterior to lambda, 5 mm posterior to bregma, and 4 mm lateral to the sagittal suture. The dura was left intact at this opening. A polyethylene (PE-50) catheter was inserted into the caudal (tail) artery for blood pressure recording and blood sampling and into the femoral vein for drug administration.

Fluid-Percussion Brain Injury

Experimental brain injury was induced using the lateral (parasaggital) fluid-percussion model that has been described extensively (McIntosh et al., 1989). The fluid-percussion injury device was connected to the animal via the Leur-Lok fitting. The device produced a 21- to 23-msec pulse of increased intracranial pressure via the rapid injection of saline into the closed cranial cavity, resulting in brief displacement and deformation of neural tissue. This pressure pulse was measured extracranially by a transducer (Gould Inc., Oxnard, California) housed in the injury device and was recorded on a storage oscilloscope (Tectronix, Inc.).

Experimental Protocol, Physiological and Neurological Monitoring

Mean arterial blood pressure (MAP), arterial blood gas concentrations, and blood pH were monitored over a 4-h postinjury observation period via the caudal arterial catheter. This catheter and the femoral venous catheter were removed and the surgical incision closed at the end of the 4 h postinjury observation period. Lidocaine hydrochloride was injected as a topical anesthetic into the incision site.A rectal thermistor probe was inserted to measure core body temperature; a needle temperature probe (Model 514, Yellow Springs Instruments, Yellow Springs, OH) was also inserted percutaneously into the right temporalis muscle, as changes in the temperature of the temporalis muscle appear to correlate closely with brain temperature in the ischemic or traumatically injured brain (Busto et al., 1987; Jiang et al., 1991). In all studies, core body and brain temperatures were maintained at control (baseline values) using a combination of heating pad and heat lamp.

At 90 min following pentobarbital anesthesia administration, all animals were subjected to fluid-percussion brain injury of moderate severity (2.4 to 2.5 atmospheres) centered over the left temperoparietal cortex. At 30 min postinjury, animals were randomly assigned to receive either naloxone hydrochloride (2.0 mg/kg in 0.2 ml followed by a constant infusion of 1.7 mg/kg/h in 0.5 ml for 4 h, $n = 8$), the TRH analog YM-14673 (1.0 mg/kg in 0.5 ml, $n = 8$), or saline vehicle (0.5 ml, $n = 8$), each administered as a slow intravenous bolus injection over 60 sec.

Chronic postinjury neurologic motor function was assessed in all animals at 24 h, and from 1 through 4 weeks postinjury. Neurologic function was evaluated using previously characterized and described neuroscore assessments (Dixon et al., 1987; McIntosh et al., 1989) by a trained observer who was unaware of each animal's treatment paradigm. The rats were scored from 4 (preinjury control status) to 0 (severely impaired) for each of the following indices: (1) contralateral forelimb flexion response during suspension by the tail (maximum score = 4), (2) decreased resistance to lateral pulsion (maximum score = 4), (3) ability to stand on an inclined plane (angle board) in the vertical and horizontal (right and left lateral) positions, with the maximal angle at which the animal could stand for a duration of 5 sec recorded (the animals were scored with regard to the change in angle from baseline data, where 0 = 4, 2.5 = 3, 5 = 2, 7.5 = 1, and 10 or more = 0, maximum score for animal placed in vertical position or horizontally facing to the right = 8), and (4) spontaneous locomotor activity, both horizontal and vertical, measured by a computerized activity monitor (Opto-Varimax, Columbus Instruments, Columbus, OH). The rats were housed within transparent cages through which 30 infrared beams passed in a horizontal plane. Interruption of the light beam identified the animal's horizontal position, while vertical motion was detected through an additional set of 15 vertical infrared beams located above the horizontal sensing plane (maximum score = 4). Activity scores were calculated by the percentage change from preinjury baseline values: 80–100% = 4, 78–88% = 3.5, 67–77% = 3, 56–66% = 2.5, 45–55% = 2, 34–44% = 1.5, 23–33% = 1, 12–22% = 0.5, 0–11% = 0. A total neurologic functional composite score (range 0 to 20) was obtained by combining the scores for the four neurobehavioral tests.

Data Analysis

All data are expressed as mean ± standard errors of the mean, except for neurologic scores, which are displayed as median scores (ordinal data). Continuous variables subjected to repeated measurements over time (e.g., cardiovascular variables) were assessed by repeated measurement analysis of variance method followed by Dunnett's test at each time point. Ordinal measurements such as neurologic scores were evaluated using nonparametric Kruskal–Wallis tests followed by individual Mann–Whitney *U*-tests. Survival differences were compared using Fisher's exact probability test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Physiological Variables

No significant differences in arterial blood gases and pH were observed between naloxone-, YM-14673-, or saline-treated animals throughout the 4-h observation period (Table 1). Fluid-percussion brain injury produced an acute but significant hypertensive response, which normalized to baseline values by 5 min postinjury (Fig. 1). Treatment with naloxone hydrochloride had no significant effect on MAP. However, treatment at 30 min postinjury with the TRH analog YM-14673 significantly elevated MAP values from 15 min postinfusion to 3 h postinjury ($p < 0.05$) (Fig. 1). Baseline brain temperature (38°C) did not change significantly following brain injury or treatment with either naloxone or YM-14673.

Neurologic Motor Function

Composite neurologic motor scores over time following lateral fluid-percussion brain injury are summarized in Figures 2–6. Saline-treated animals displayed a moderate to severe neurologic deficit in all of the motor-function tests (median score at 24 h = 10). Individual motor function test scores improved slightly over

TABLE 1. ARTERIAL BLOOD GASES AND pH FOLLOWING EXPERIMENTAL FLUID-PERCUSSION BRAIN INJURY AND ADMINISTRATION OF SALINE, NALOXONE HYDROCHLORIDE, OR YM-14673[a]

		Preinjury	*30 min*	*2 h*	*4 h*
PO_2	Saline	84 ± 9	81 ± 9	85 ± 12	83 ± 10
	Naloxone	82 ± 5	85 ± 4	90 ± 4	92 ± 4
	YM-14673	82 ± 8	81 ± 5	82 ± 5	87 ± 9
PCO_2	Saline	42 ± 13	46 ± 7	43 ± 6	47 ± 3
	Naloxone	46 ± 5	47 ± 4	44 ± 5	45 ± 4
	YM-14673	43 ± 4	50 ± 3	48 ± 5	48 ± 6
pH	Saline	7.36 ± 0.02	7.36 ± 0.04	7.37 ± 0.03	7.37 ± 0.04
	Naloxone	7.36 ± 0.04	7.36 ± 0.02	7.40 ± 0.10	7.38 ± 0.03
	YM-14673	7.34 ± 0.02	7.35 ± 0.02	7.34 ± 0.02	7.33 ± 0.03

[a] All values expressed as mean ± SEM. $n = 8$ for each treatment group.

the first 2 weeks and then stabilized (median score at 1 week = 12 and at 2 weeks = 14); a significant motor deficit was still observed at 3 and 4 weeks postinjury (median score = 14.5 for weeks 3 and 4). Of the individual motor function scores, angleboard and contralateral forelimb flexion were the most sensitive indicators of improved neurologic motor function with pharmacologic treatment. While all individual motor function tests may not have the sensitivity to detect small neurologic improvements following treatment, when individual scores are summated and expressed as a composite median score, small improvements in motor function can be readily detected. Thus we have shown here and elsewhere that composite scores provide a sensitive indicator of neurologic outcome (McIntosh et al., 1988b, 1989; Vink et al., 1990).

Treatment with naloxone hydrochloride had no significant effect on neurologic motor scores measured at 24 h postinjury. However, by 1 week postinjury, naloxone-treated animals showed a significant improvement in composite motor scores (median = 16 vs. 12 for controls, $p < 0.05$). Naloxone-treated animals continued to improve over the 4-week study period, and by week 4 demonstrated median neurologic composite score of 18.5 out of a maximum possible score of 20 (compared to 14.5 for controls, $p < 0.05$). Like naloxone, animals treated at 30 min postinjury with YM-14673 also did not show any improvement in neurologic function at 24 h postinjury (median score = 9). However, by 1 week, YM-14673-treated animals showed a significant improvement in neurologic function (median composite score = 15.5 vs. 12 for control, $p < 0.05$). Neurologic scores continued to improve over time in YM-14673-treated animals, to reach a score of 20

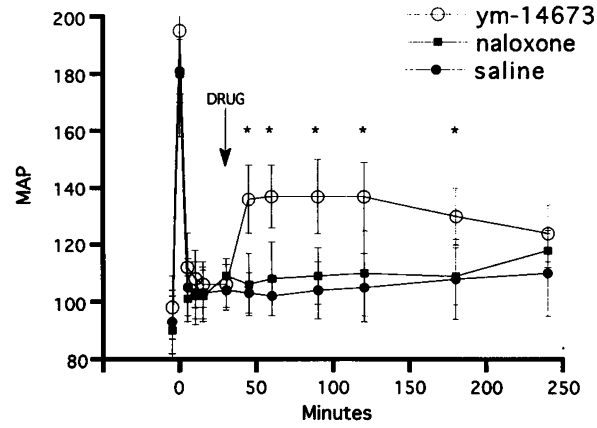

FIG. 1. Changes in mean arterial blood pressure (MAP) following fluid-percussion brain injury and intravenous treatment at 30 min postinjury with either naloxone hydrochloride (■, 2 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (○, 1.0 mg/kg, $n = 8$), or saline (●, equal volume, $n = 8$). *$p < 0.05$ when compared to other treatment groups.

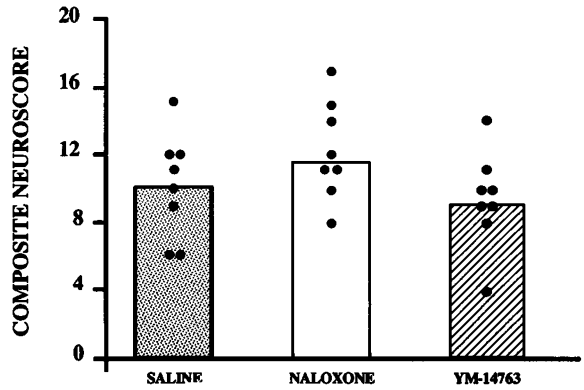

FIG. 2. Individual composite functional neurologic scores obtained at 24 h following fluid-percussion brain injury and treatment at 30 min postinjury with naloxone hydrochloride (2.0 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline (equal volume, $n = 8$). *$p < 0.05$ when compared to saline-treated controls.

(virtually indistinguishable from normal uninjured animals) by 3 and 4 weeks postinjury ($p < 0.01$ compared to control scores). No statistical differences were observed between YM-14673- and naloxone-treated animals at any time point.

All saline-, naloxone-, and YM-14673-treated animals survived up to 4 weeks following injury and no significant differences were observed in mortality among groups.

DISCUSSION

The present study demonstrates that the opioid antagonist naloxone, when administered at relatively high doses (2.0 mg/kg; 1.7 mg/kg/h) following experimental fluid-percussion brain injury significantly improves neurologic recovery. Naloxone administration in this study had no significant effect on cardiovascular variables during the first 4 h postinjury, similar to what we have observed previously with the opioid receptor antagonist nalmefene, which also shows a beneficial effect of posttraumatic motor function after traumatic brain injury (Vink et al., 1990). Thus, the improvement in neurologic scores following administration of opioid antagonists in models of brain injury does not appear to be related to the effects of naloxone on peripheral or CNS cardiovascular systems. Since our model of fluid-percussion brain injury is associated with significant reductions in regional cerebral blood flow (rCBF) (Yamakami and McIntosh, 1989, 1991),

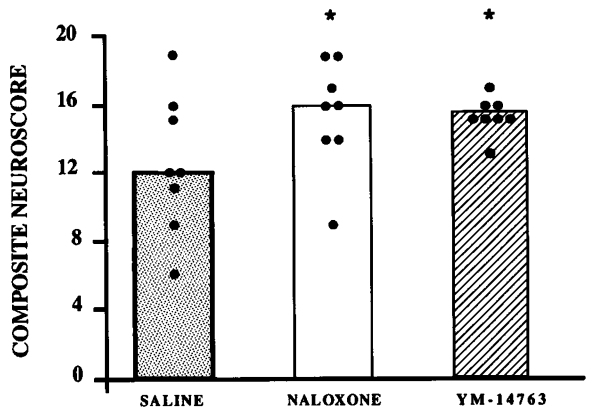

FIG. 3. Individual composite functional neurologic scores obtained at 1 week following fluid-percussion brain injury and treatment at 30 min postinjury with naloxone hydrochloride (2.0 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline (equal volume, $n = 8$). *$p < 0.05$ when compared to saline-treated controls.

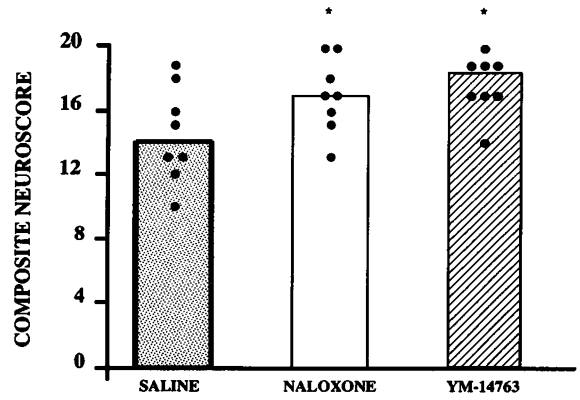

FIG. 4. Individual composite functional neurologic scores obtained at 2 weeks following fluid-percussion brain injury and treatment at 30 min postinjury with naloxone hydrochloride (2.0 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline (equal volume, $n = 8$). $*p < 0.05$ when compared to saline-treated controls.

reminiscent of those that occur following clinical brain injury (Bouma et al., 1991), and since it has been demonstrated that naloxone administration has beneficial effects on regional blood flow in models of acute spinal trauma (Faden et al., 1981; Flamm et al., 1982) and cerebral ischemia (Faden et al., 1982; Turner et al., 1984; Phillis et al., 1985), it is possible that the beneficial effects of this compound on neurologic function may be due to an improvement in posttraumatic rCBF. Current studies in our laboratory employing rCBF measurements following naloxone administration will address this possibility.

Our results in traumatic brain injury support those of previous studies suggesting that administration of high dose naloxone is beneficial in models of spinal cord injury (Faden et al., 1981; Flamm et al., 1982; Holaday and Faden, 1980; Young et al., 1981) and cerebral ischemia (Baskin and Hosobuchi, 1981; Faden et al., 1982; Hosobuchi et al., 1982; Phillis et al., 1985; Stokes et al., 1984; Turner et al., 1984; Zabramski et al., 1984). Our results also confirm and extend those of Hayes et al. (1983), who originally observed an improvement in physiological parameters following naloxone pretreatment (10 mg/kg) prior to the induction of midline fluid-percussion brain injury in the cat, and later observations that ip pretreatment with naloxone (20 mg/kg) significantly improved long-term neurologic deficits after midline fluid-percussion brain injury in the rat (Hayes et al., 1990). Importantly, it should be noted that Hayes and colleagues (1990) reported that pretreatment with low doses of naloxone (0.1 or 1.0 mg/kg), which primarily affects μ-opioid receptors,

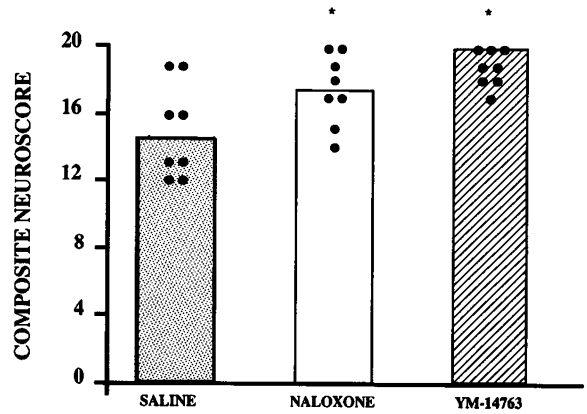

FIG. 5. Individual composite functional neurologic scores obtained at 3 weeks following fluid-percussion brain injury and treatment at 30 min postinjury with naloxone hydrochloride (2.0 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline (equal volume, $n = 8$). $*p < 0.05$ when compared to saline-treated controls.

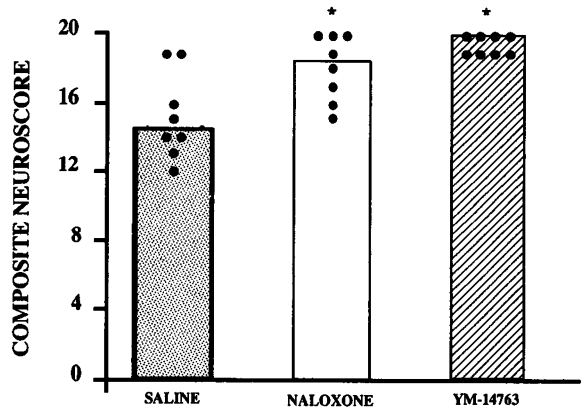

FIG. 6. Individual composite functional neurologic scores obtained at 4 weeks following fluid-percussion brain injury and treatment at 30 min postinjury with naloxone hydrochloride (2.0 mg/kg followed by 1.7 mg/kg/h for 4 h, $n = 8$), YM-14673 (1.0 mg/kg, $n = 8$), or saline (equal volume, $n = 8$). $*p < 0.05$ when compared to saline-treated controls.

significantly exacerbated neurologic deficits associated with brain injury, whereas higher doses which can block κ-opioid receptors may be efficacious in the treatment of brain trauma.

Taken together, these data suggest the possibility that some classes of endogenous opioids (mu ligands) may protect against long-term deficits produced by fluid-percussion brain injury to the rat, while others (κ ligands) may exert deleterious effects. The κ-opioid receptor agonist dynorphin has been previously proposed to be the predominant pathologic endogenous opioid in traumatic spinal cord injury (Faden et al., 1988b; Faden, 1990; Przewlocki et al. 1983; Long et al., 1987, 1988) and cerebral ischemia (Andrews et al., 1989). In experimental models of traumatic brain injury, (1) dynorphin has been shown to accumulate in brain regions demonstrating the most significant reductions in rCBF and histopathologic damage (McIntosh et al., 1987b), (2) central and peripheral administration of dynorphin and other κ-agonists can exacerbate posttraumatic alterations in cerebrovascular function and neurologic outcome (McIntosh et al., 1988a), and (3) opioid antagonists with enhanced activity at κ-opioid receptors have been shown to improve cerebrovascular, physiologic, neurochemical, metabolic, and behavioral outcome (McIntosh et al., 1987a; Vink et al., 1990, 1991). It is possible, then, that the efficacy of naloxone observed in the present study is due, in part, to its inhibitory effects on pathologic κ-opiate systems.

Endogenous opioids have been recently reported to interact with the excitatory amino acid (EAA) neurotransmitters glutamate and aspartate, and it is possible that the beneficial effects of opioid antagonists, including those observed for naloxone in the present study, may be mediated through alterations of EAA-induced excitotoxicity. Several studies have suggested a role for opioid receptors in *N*-methyl-D-aspartate (NMDA) receptor-mediated events in the hippocampus, including long-term potentiation and cognitive function (Derrick et al., 1991; Moises and Walker, 1985; Zieglansberger et al., 1979). Dynorphin-induced hindlimb paralysis and loss of tail-flick reflex have both been shown to be attenuated by NMDA antagonists (Bakshi and Faden, 1990; Bakshi et al., 1990; Caudle and Isaac, 1988; Stewart and Isaac, 1989; Isaac et al., 1990). Intrathecal dynorphin administration causes depletion of tissue levels of glutamate and aspartate (Bakshi and Faden, 1990), while Faden (1992) has shown that both dynorphin A-1-17 and the inactive dynorphin A-2-17, when microinjected into the hippocampus, produce a marked increase in extracellular concentrations of glutamate and aspartate. Although Hudson et al. (1991) have suggested that the κ-opiate agonist U50,488H attenuates NMDA-induced brain injury in neonatal rats, others have shown that κ-opiate receptor ligands do not function as EAA antagonists (Berry et al., 1984; Parsons et al., 1986). Moreover, Choi and Viseskul (1988) have demonstrated that the long-acting opiate antagonist naltrexone produces a concentration-dependent reduction in NMDA neurotoxicity in murine cortical cell cultures. Because dynorphin can stimulate release of glutamate, it is possible that opioid antagonists such as naloxone may play a role in reducing post-traumatic excitotoxicity through an opiate-EAA interaction. This hypothesis awaits confirmation.

Our observations with the TRH analog YM-14673 confirm previous reports that TRH or TRH analogs improve outcome following experimental spinal cord trauma (Faden, 1989; Faden et al., 1984, 1988a) or traumatic brain injury (Fukuda et al., 1979; Manaka and Sano, 1978; McIntosh et al., 1988b; Vink et al., 1988), and support the hypothesis that TRH analogs preserving the C-terminus are effective in various models of CNS trauma. Unlike naloxone, administration of YM-14673 induced a significant increase in MAP in brain-injured animals, consistent with previous reports using TRH analogs (Faden, 1989; McIntosh et al., 1988b). Although these pressor effects of TRH analogs may contribute to the experimental efficacy of these compounds, we have previously shown that pharmacologically induced increases in MAP (using dopamine) do not cause similar improvements in regional cerebral blood flow or reductions in histopathologic damage to those observed following treatment with TRH analogs. Although previous work with this compound in both spinal cord and traumatic brain injury observed optimal beneficial effects of the 1.0 mg/kg dose on neurologic motor scores at 2 weeks (median composite scores = 18.5), by extending the study period to 4 weeks postinjury, we were able to observe in the present study that animals treated with this 1.0 mg/kg dose showed the best neuroscores possible (median scores = 20), virtually indistinguishable from normal (uninjured) animals. Few pharmacologic compounds in our laboratory have elicited such a complete neurologic improvement following fluid-percussion brain injury. Perhaps the increased benefit of TRH analogs are due to the fact that they are *less* selective at opioid receptors and can also affect leukotriene and PAF systems, which have both been implicated in the pathophysiology of CNS trauma (Hall et al., 1986; Faden and Salzman, 1992; Faden and Tzendzalian, 1992). Although most treatments that are effective in reducing chronic posttraumatic deficits are also effective acutely, the results of the present study suggest that there is a delay in the neurologic improvement in the naloxone- and YM-14673-treated animals. Although these findings are intriguing, the mechanisms underlying these phenomena are unknown at present.

Following mild to moderate clinical head injury, patients often exhibit marked impairment of learning, information processing, or memory without any demonstrable neurologic motor deficit (Alves and Jane, 1985; Levin, 1991). Although the present study suggests that opiate antagonists may be efficacious in reversing posttraumatic motor dysfunction, nothing is known concerning the ability of these compounds to improve posttraumatic cognitive deficits. Future studies will focus on the ability of these drugs to attenuate cognitive dysfunction associated with experimental brain injury.

Our results suggest that both the nonselective antagonist naloxone and the long-acting, centrally-active TRH analog YM-14673 can induce significant and prolonged improvement in neurologic motor function when administered in the posttraumatic period following experimental fluid-percussion brain injury in the rat. Future studies will focus on the mechanisms underlying this pharmacologic improvement and evaluate the critical window for posttraumatic therapeutic intervention with opiate antagonists and similar compounds.

ACKNOWLEDGMENTS

This work was supported, in part, by an NIH R01 Grant NS26818 and a Veterans Administration Merit Review Grant 74R. We thank Laura Meehan for preparation of this manuscript. In these studies, we carefully adhered to the animal welfare guidelines set forth in the "Guide for the Care and Use of Laboratory Animals," U.S. Department of Health and Human Services Pub. No. 85-23, 1985.

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