

Research report

Chronic failure in the maintenance of long-term potentiation following fluid percussion injury in the rat

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Abstract

Traumatic brain injury (TBI) can produce chronic cognitive learning/memory deficits that are thought to be mediated, in part, by impaired hippocampal function. Experimentally induced TBI is associated with deficits in hippocampal synaptic plasticity (long-term potentiation, or LTP) at acute post-injury intervals but plasticity has not been examined at long-term survival periods. The present study was conducted to assess the temporal profile of LTP after injury and to evaluate the effects of injury severity on plasticity. Separate groups of rats were subjected to mild (1.1–1.4 atm), moderate (1.8–2.1 atm), or severe (2.2–2.7 atm) fluid percussion (FP) injury (or sham surgery) and processed for hippocampal electrophysiology in the first or eighth week after injury. LTP was defined as a lasting increase in field excitatory post-synaptic potential (fEPSP) slope in area CA1 following tetanic stimulation of the Schaffer collaterals. The fEPSP slope was measured for 60 min after tetanus. Assessment of LTP at the acute interval (6 days) revealed modest peak slope potentiation values (129–139%), which declined in each group (including sham) over the hour-long recording session and did not differ between groups. Eight weeks following injury, slices from all groups exhibited robust maximal potentiation (134–147%). Levels of potentiation among groups were similar at the 5-min test interval but differed significantly at the 30- and 60-min test intervals. Whereas sham slices showed stable potentiation for the entire 60-min assessment period, slices in all of the injury groups exhibited a significant decline in potentiation over this period. These experiments reveal a previously unknown effect of TBI whereby experimentally induced injury results in a chronic inability of the CA1 hippocampus to *maintain* synaptic plasticity. They also provide evidence that sham surgical procedures can significantly influence hippocampal physiology at the acute post-TBI intervals. The results have implications for the mechanisms underlying the impaired synaptic plasticity following TBI. © 2000 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Traumatic brain injury (TBI) is associated with a number of neurochemical, neurophysiological, and behavioral sequelae. Patients showing “good” recovery after injury may exhibit lasting neuropsychological deficits. In patients showing good Glasgow outcome scores, tests sensitive to attention and concentration, information processing, and cognitive endurance indicated deficits [30]. The most sensitive measure of neuropsychological deficit showed little

correlation to time since injury, indicating that severity of some deficits may be independent of recovery time [30]. A number of animal models have been developed to investigate basic mechanisms of head injury. All models are capable of reproducing at least some of the anatomical and behavioral changes seen in human head injury. Cortical impact and fluid percussion (FP) injury are well-known for their ability to model the impaired learning and memory seen in the human condition. The severity of the experimental insult (measured in atmospheres for FP injury and depth/velocity for impact models) determines the severity of neuroanatomical, neurochemical, and neurological outcomes [8,15,19]. At the behavioral level, experimental trauma results in both sensorimotor and cognitive deficits

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[3,10,11,17,19,27]. Moderate FP trauma results in some pathology in hippocampal CA3 and dentate gyrus [7] as well as behavioral deficits on tasks sensitive to hippocampal function [10]. The physiological changes underlying behavioral deficits may be subtle. Indeed, some models of trauma, including the vertex FP injury, include cognitive deficits in the absence of overt hippocampal neuropathology [17].

Investigators have begun to employ electrophysiological measures of synaptic plasticity to examine the functional nature of hippocampal circuits in the presence or absence of overt necrosis. TBI of moderate severity results in disturbances of hippocampal electrophysiology and a loss of experimentally induced synaptic plasticity. Excitability of hippocampal CA1 cells is altered by TBI [4,21,24] and the ability of tetanic stimulation to potentiate CA1 responses is reduced in the acute post-traumatic period [21,24]. Miyazaki et al. [21] reported that trauma resulted in decreased thresholds and increased amplitudes of population spikes and a reduction in the ability of tetanic stimulation to enhance population spike amplitude and field potential slope. In the *in vivo* preparation, deficiencies in long-term potentiation (LTP) last as long as 15 days after FP injury [24].

Recent studies have proven the hippocampal slice technique to be adequate in addressing the effects of TBI. Sick et al. [26] demonstrated a loss of plasticity in hippocampal slices taken from traumatically injured animals. Slice field excitatory post-synaptic potentials (fEPSPs) slope potentiation was dramatic in sham animals but greatly reduced in moderately injured (1.7–2.1 atm) animals up to 2 days following injury. In another experiment, an injury of relatively severe magnitude (2–4 atm) resulted in complete prevention of LTP in the CA1 region measured 1–2 days after injury [4]. However, TBI did not affect long-term depression [4].

No study of the electrophysiological effects of TBI has taken full advantage of the severity continuum afforded by animal models. Animal models of injury are designed specifically to implement a large range of injury severities in order to model clinical patterns of trauma. Increasing severity in animal models of TBI has been associated with increasing disturbances in neuronal physiology and increasing magnitude of cognitive deficits [13,19,22,25]. While even mild traumatic injury can result in damage to hippocampal dentate hilus [11,16], moderate and severe injuries result in increased injury to other structures including cortex, thalamus, hypothalamus, hippocampal CA3 [7], and brainstem [19]. Increments in injury severity should be associated with increasing functional disturbances in neuronal circuitry.

In light of previous observations of synaptic plasticity dysfunction following injury and the lack of data concerning both severity of injury and chronic recovery of function, the current study was undertaken to shed light on the physiological consequences of TBI. Increasing severity of

injury is expected to result in progressive compromise of synaptic plasticity in the acute period following injury. Furthermore, it is expected that only the most severe injuries will result in chronic impairments in synaptic plasticity.

2. Materials and methods

2.1. Subjects

Slices from 64 male Sprague–Dawley rats were tested for electrophysiological deficits following lateral FP injury or sham surgery. Hippocampi were extracted from rats at 6 days or 8 weeks following surgery. Each animal was subjected to sham surgery or one of three levels of injury. Eight groups of rats were included in the experiment: SHA-1 week (sham, $n = 8$), MIL-1 week (mild, $n = 8$), MOD-1 week (moderate, $n = 8$), SEV-1 week (severe, $n = 7$), SHA-8 week (sham, $n = 8$), MIL-8 week (mild, $n = 8$), MOD-8 week (moderate, $n = 8$), and SEV-8 week (severe, $n = 8$). All animals were housed before and after surgery under a 12:12 day:night cycle (lights on at 0600 h) with *ad libitum* food and water. All surgical procedures were conducted under the guidelines of the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of Miami Animal Research Committee.

2.2. Surgery

FP brain injury was induced as previously described [7] with a few modifications. Each animal was anesthetized with 3.33 ml/kg equithesin supplemented as necessary. Upon sufficient anesthetic state, the animal's head was shaved and the animal was placed in a stereotaxic frame. An incision was made along the midline scalp and the skin and fascia were retracted. A round craniotomy (4.8 mm diameter) was made over the right parietal cortex with approximate center coordinates of 3.8 mm posterior and 2.5 mm lateral to bregma. A small plastic tube (constructed from a Luer-lock needle) was placed over the intact dura and bonded to the skull with Loctite tissue adhesive (Ted Pella, Redding, CA). Upon drying, the bond was reinforced with copious amounts of dental acrylic. After the dental acrylic was set, thermistors were placed in the rectum and the temporalis muscle. Temporalis muscle temperature has been shown to give an indirect but reliable estimate of brain temperature, which is crucial in the outcome of TBI [see Ref. [6]]. Rectal and temporalis temperatures were allowed to stabilize over a 10-min period, with the rectal thermostat set to $37 \pm 0.5^\circ\text{C}$ and the temporalis thermostat set to $36.5 \pm 0.5^\circ\text{C}$. Heat was maintained by two lamps (standard, white light) wired to the thermostats and aimed at the head and trunk of the animal.

Following temperature stabilization, the animal was removed from the stereotaxic frame and the injury tube atop the animal's head was attached to a male Luer fitting on a fluid percussive device. The main portion of the apparatus consisted of a Plexiglas cylinder filled with saline. One end of the device was fitted with a Luer interface and a pressure transducer while the other was capped by a moveable piston on rubber O-rings. A pendulum (set at various heights to induce injuries of various pressures) struck the piston and created a pressure pulse wave through the Plexiglas cylinder. A small bolus of saline was introduced, for a period of about 20 ms, into the extradural space of the attached rat. A microcomputer recorded the injury pressure in a voltage deflection that was later converted to atmospheres. Injury pressures (mean \pm S.E.M.) for the various groups were as follows: MIL-1 week: $1.20 \pm .02$, MIL-8 week $1.15 \pm .05$, MOD-1 week: $1.92 \pm .03$, MOD-8 week: $1.91 \pm .03$, SEV 1-week: $2.35 \pm .02$, SEV 8-week: $2.32 \pm .06$. Animals in the sham groups underwent all surgical procedures excluding attachment to the fluid percussive device and delivery of the pressure pulse.

Following injury, each animal was removed from the device and the injury tube and dental cap were removed from the skull with a pair of rongeurs. Care was taken during removal to avoid any skull or tissue damage. After returning the animal to the stereotaxic frame, gelfoam was applied to the craniotomy and the scalp was sutured closed. Each animal was returned to the home cage after surgery and to the colony room the next day.

2.3. Slice harvesting

Slices were harvested either 6 days or 8 weeks after injury, 1 day after the animals were tested for cognitive deficits in the Morris water maze [data presented in Ref. [25]]. Testing in the water maze included 16 hidden platform trials and 8 visible platform trials for each animal, conducted over 1 day. Measures of mean latency to reach the platform under each condition were correlated, for each animal, with the plasticity shown by hippocampal slices harvested 24 h later. For harvesting, each rat was anesthetized with 50 mg/kg sodium pentobarbital given i.p. After induction of anesthesia, the rat was placed on ice for 10 min to lower head and body temperature. The rat was then decapitated and the head was placed on ice. The rat's skull was dissected over ice and the brain was removed rapidly and placed in ice-cold aCSF (containing, in mM: 126 NaCl, 3.0 KCl, 2.0 CaCl₂, 2.0 MgSO₄, 26 NaHCO₃, 1.25 NaH₂PO₄, 10 glucose). The brain was bisected hemispherically and the right hemisphere (ipsilateral to the injury) was glued to a pedestal with cyanoacrylate adhesive and placed in a chamber containing cold aCSF. A vibroslicer (Model 752M, World Precision Instruments, Sarasota, FL) was used to slice 400- μ m thick sections through the hemisphere. Sections were transferred to a

Petri dish containing aCSF, where the hippocampus was dissected out. Hippocampal slices were transferred to another holding dish containing oxygenated aCSF (95% O₂ and 5% CO₂). Slices were allowed to sit undisturbed for a minimum of 1 h before transfer to the testing chamber.

2.4. Hippocampal electrophysiology

For testing, each slice was transferred to an interface-type chamber and placed on nylon netting in aCSF heated to 35–36°C. Electrodes were placed in the Schaffer collaterals and stratum radiatum of CA1 under a stereoscope. The Schaffer collaterals were stimulated with biphasic 0.3 ms constant-current pulses delivered via a bipolar tungsten electrode attached to a stimulus isolator (Model A365, World Precision Instruments, Sarasota, FL). The fEPSPs were sampled from the stratum radiatum via a glass micropipette filled with 150 mM NaCl solution. Signals were filtered at a 5-kHz ceiling and amplified 100 times by a BMA830 amplifier (CWE, Ardmore, PA). After stabilization of the fEPSP over at least 10 min of observation, an input/output (I/O) function was obtained over a range of 100–1000 μ A in 100 μ A steps. All electrophysiological recordings were initiated within 6 h of decapitation; analyses confirmed that slices tested across this 6 h window did not differ on any measured parameter (data not shown). After collection and analysis of the initial I/O series, a stimulus intensity was chosen that gave approximately 1/2 the maximal recorded fEPSP slope. This stimulus intensity was used throughout the baseline and post-tetanic measures. A 10-min baseline record was taken with a stimulus frequency of 0.033 Hz (one stimulus every 30 s). If baseline responses were stable, tetanic stimulation was applied. One-hundred Hertz stimulation was applied for 1 s, at the same intensity as the baseline stimuli. Test stimuli then were resumed at 0.033 Hz and continued for 1 h. Additional I/O functions were acquired at 30 and 60 min after tetanus.

All stimulus applications and signal acquisitions were controlled with a personal computer running the Experimenter's Workbench software system (Datawave Technologies, Longmont, CO). Each analog signal was collected at 30 kHz and stored to disk for later analysis. The slope of each field potential was calculated as the average rate of change in voltage over time in the rising segment of the fEPSP, measured between 20% and 80% of the peak. Field potentials were evoked at the test stimulus intensity and slope was calculated off-line for each stimulus delivery. Potentiation was assessed from fEPSPs evoked 5, 30, and 60 min after tetanus.

2.5. Statistical analyses

A maximum of two slices were examined from each animal. In cases in which data were collected from two

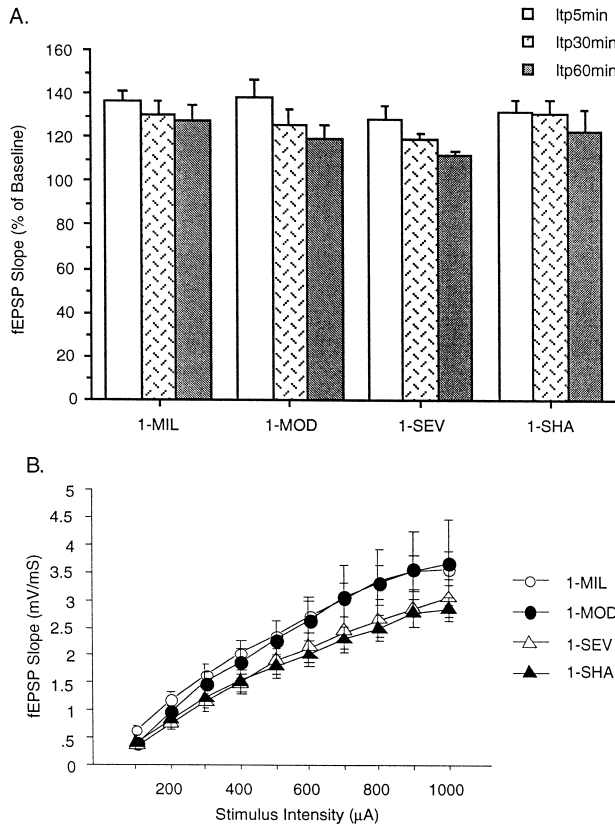


Fig. 1. Slice electrophysiology at 6 days after injury or sham surgery. (A) The figure gives the mean (\pm S.E.M.) potentiation at each post-tetanic sampling point. The mean slope of 10 samples taken at each time point is expressed as a function of the percentage of the mean of 10 baseline samples. The interaction of group and time effects was not significant. (B) The graph depicts the mean (\pm S.E.M.) baseline I/O function of the fEPSP slope across 10 stimulation intensities. Slices from all groups exhibited increased fEPSP slope with increasing stimulus intensity. Interaction between group and intensity effects was not significant.

slices from a particular animal, the data were averaged before being analyzed further; thus, each animal comprised a single “case” in the dataset. If a slice exhibited a pathological depression in fEPSP slope following tetanus (defined as mean fEPSP slope of less than 75% of baseline), then data from the slice were eliminated from analysis. Ten baseline measures of fEPSP slope were averaged to give a measure of pre-tetanus synaptic strength. Sets of 10 potentials were collected at 5-, 30-, and 60-min time points. For each slice, the average slope value of each post-tetanic set was converted to a percentage of the baseline mean. A pre-tetanus I/O function relating stimulation intensity to fEPSP slope was collected. Post-tetanus I/O functions were collected in which fEPSP slope was normalized as a percentage of the maximum slope taken during the pre-tetanus I/O. I/O curves and post-tetanus potentiation values were compared among groups using a repeated measures ANOVA. Pre-tetanus fEPSP slopes were compared among groups with a simple ANOVA.

Finally, correlational analyses were conducted with both the electrophysiological data from this study and the be-

havioral data from a previous experiment performed with the same subjects [25]. These correlations were computed on a within-animal basis between scores on the water maze task and potentiation values in the slice experiments. Spearman’s rank-order correlation coefficients were computed between LTP measures and water maze measures of latency to escape to a hidden or visible platform (typical measures of learning in this task).

3. Results

3.1. Hippocampal electrophysiology and synaptic plasticity 1 week after injury

Fig. 1A shows group data for percent change in the fEPSP observed at 5, 30, and 60 min following tetanization from 31 animals. Slices from all groups of animals exhibited LTP that was maximal at 5 min, where it reached 129–139% of baseline. No group differences were observed in potentiation at the 5-, 30-, or 60-min post-tetanus interval (all $F < 1$; all $p > 0.49$). As seen in Fig. 1A, potentiation of the fEPSP slope declined over the hour of

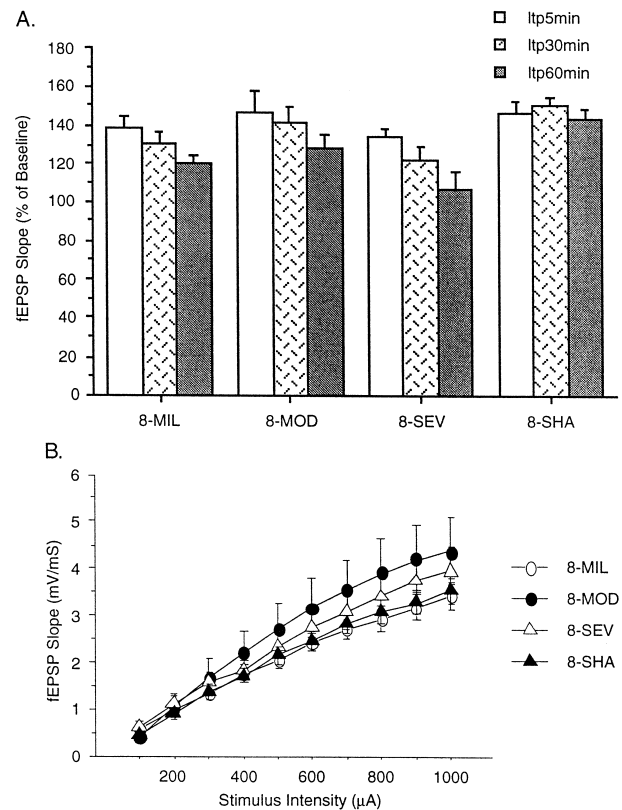


Fig. 2. Slice electrophysiology at 8 weeks after injury or sham surgery. (A) The figure gives the mean (\pm S.E.M.) potentiation at each post-tetanic sampling point. The interaction of group and time effects was significant, indicating that group inclusion affected the time course of potentiation. (B) The graph depicts the mean (\pm S.E.M.) baseline I/O function of the fEPSP slope across 10 stimulation intensities. Slices from all groups exhibited increased fEPSP slope with increasing stimulus intensity. Interaction between group and intensity effects was not significant.

observation ($F_{2,54} = 13.24$; $p < 0.0001$) but groups did not differ in the degree of decline (group \times time interaction: $F_{6,54} < 1$; $p > 0.61$).

Fig. 1B presents group data for the pre-tetanus I/O function. Increasing intensity of stimulation reliably produced an increase in fEPSP slope across groups ($F_{9,243} = 151.549$; $p < 0.0001$) but there was no group difference in the mean fEPSP produced during the series ($F_{3,27} = 1.12$; $p > 0.36$) and no interaction between group and stimulation intensity ($F_{27,243} < 1$; $p > 0.76$). Finally, no group difference was seen in the baseline potential. Baseline stimulation resulted in comparable fEPSP slopes in all groups ($F_{3,27} < 1$; $p > 0.57$).

3.2. Hippocampal electrophysiology and synaptic plasticity 8 weeks after injury

Fig. 2A depicts the mean fEPSP potentiation observed following tetanus for the 8-week animals over the 5-, 30-, and 60-min observation periods. The mean maximal potentiation observed at the 5-min test interval ranged from

134% to 147%. Potentials in slices from all *injured* groups decreased substantially over the 60-min observation period, whereas potentials in the sham group remained stable. This group difference in the apparent failure of LTP “maintenance” was confirmed statistically: analyses revealed a significant interaction between group and time period ($F_{6,56} = 2.66$; $p = 0.025$). Follow-up analyses indicated significant main effects of time in each injured group (all $p < 0.01$) but not in the sham group ($p > 0.35$). More importantly, group potentiation values did not differ at 5 min ($F_{3,28} < 1$; $p > 0.55$) but differed significantly at both the 30-min timepoint ($F_{3,28} = 3.34$; $p < 0.05$) and the 60-min timepoint ($F_{3,28} = 5.285$; $p < 0.01$).

In contrast to the TBI-associated group differences in LTP maintenance, there was no group difference in the pre-tetanus I/O series (mean I/O values for the 8-week groups are depicted in Fig. 2B). Increasing intensity of stimulation produced an increase in fEPSP slope across groups ($F_{9,252} = 184.05$; $p < 0.0001$). The mean fEPSP produced during the series did not differ among groups ($F_{3,28} < 1$; $p > 0.52$) and there was no interaction between

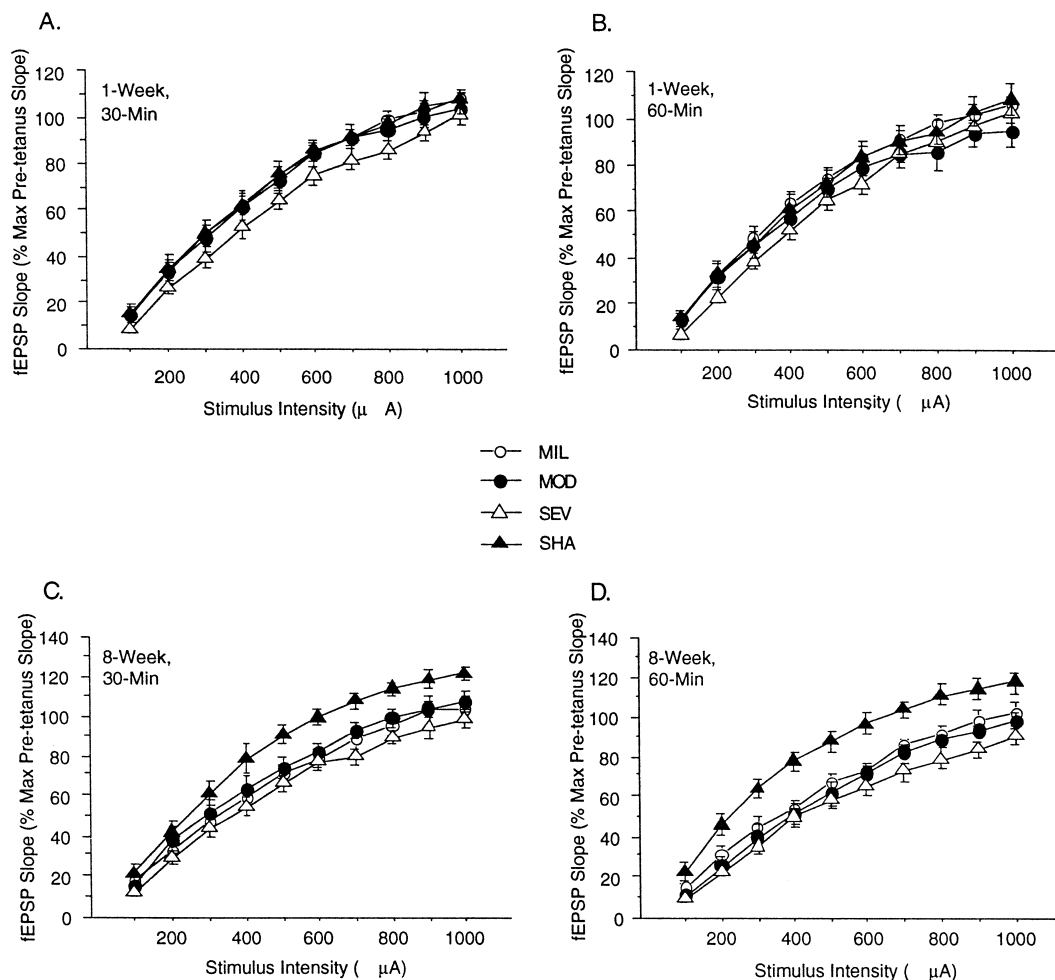


Fig. 3. I/O functions at 30 and 60 min after tetanus. In the first week, groups exhibited the same level of potentiation in the I/O function at 30 (A) and 60 (B) min. In the eighth week, the sham group exhibited greater potentiation of the I/O than the injured groups at both 30 (C) and 60 (D) min after tetanus.

Table 1
Correlations between LTP and water maze measures^a

Group	Correlation between LTP and hidden platform latency	Correlation between LTP and visible platform latency
1-week injured animals	-0.073 ($p = 0.7316$)	-0.095 ($p = 0.6619$)
1-week sham animals	-0.357 ($p = 0.3447$)	-0.619 ($p = 0.1015$)
8-week injured animals	-0.105 ($p = 0.6138$)	-0.414 ($p = 0.0521$)
8-week sham animals	0.036 ($p = 0.9303$)	0.714 ($p = 0.0588$)

^aSanders et al. [25].

the group and stimulation intensity factors ($F_{27,252} = 1.177$; $p > 0.2$). Finally, groups did not differ in the baseline (half-maximal) fEPSP slope to which post-tetanic measures were compared ($F_{3,28} < 1$; $p > 0.63$).

3.3. Effects of tetanic stimulation on I/O function

I/O functions were taken 30 and 60 min after tetanus and are shown in Fig. 3. The fEPSP responses were normalized by expression as a percentage of the maximum fEPSP slope taken during the pre-tetanus I/O function. In the first week after injury, slices from all groups of animals exhibited similar I/O functions at 30 min after tetanus ($F_{3,27} = 1.305$; $p > 0.29$; Fig. 3A) and at 60 min after tetanus ($F_{3,27} < 1$; $p > 0.48$; Fig. 3B).

At the 8-week time point, groups differed significantly on the I/O measure taken at 30 min ($F_{3,28} = 6.688$; $p < 0.01$; Fig. 3C). The difference among groups was more dramatic at the 60-min point ($F_{3,27} = 13.356$; $p < 0.0001$; Fig. 3D). The sham group, in particular, showed an enhanced response over a wide range of the I/O function following tetanus.

3.4. The relationship between hippocampal synaptic plasticity and learning in the Morris water maze after injury

The correlations between LTP and water maze performance are presented in Table 1. Separate correlations were conducted for injured and sham groups. Injured animals showed a profound impairment in hidden platform learning in the first week after injury [25] without showing a concordant impairment in hippocampal CA1 LTP. Traumatized animals showed an injury-related deficit on all measures of learning in the first week, including a non-spatial cued platform task. However, injured animals showed no deficit, when compared to sham animals, in LTP measures taken just 24 h later. No significant correlations were found between behavior and physiology among the 1-week sham animals.

Correlations conducted on the 8-week data are only slightly different from those conducted on the 1-week data. A trend existed among injured rats for a significant relationship between LTP and visible platform performance, but this task is not believed to be dependent on hippocampal function. Additionally, sham animals showed an oppo-

site trend (still non-significant) in the relationship between LTP and visible platform learning whereby greater plasticity was associated with longer latencies in the water maze task. Finally, no relationship was found in the injured or sham animals between hippocampal synaptic plasticity and performance in the hidden platform maze (a task shown to be dependent on hippocampal integrity).

4. Discussion

This paper reports the novel finding that FP brain injury produces chronic perturbation in the maintenance of synaptic plasticity. At 8 weeks after surgery, severely injured animals exhibited impaired synaptic plasticity when compared to sham controls. Additionally, all injury intensities were associated with a time-dependent decay in LTP. This result implies an impairment in the maintenance of synaptic plasticity following FP injury. Slices from sham controls showed no such impairment in maintenance at 8 weeks after surgery. At 30 and 60 min after potentiation, slices from 8-week sham animals exhibited a robust elevation of the I/O function (without change in the shape of the function). The I/O data indicate that synaptic responses were potentiated over a wide range of stimulus intensities.

The data in this study indicate a disturbance in the ability of slices to maintain LTP in the chronic period following injury. The deficit seems particular to the maintenance phase, as measures taken 5 min after tetanus showed no impairment in potentiation. In light of this finding, it is likely that trauma leaves mechanisms essential to LTP induction, or at least those mechanisms involved in post-tetanic potentiation, intact (at least in the chronic post-traumatic period). Elements shown to be essential for the induction of hippocampal synaptic plasticity include NMDA receptor function, normal magnesium trafficking, and normal calcium influx. Additionally, transmitter systems such as the cholinergic, noradrenergic, and opioidergic systems have been implicated in the induction of LTP [Refs. [12,28,31], respectively]. It is likely that disturbances in these transmitter systems are not responsible for the effect reported here.

The data presented in this paper implicate pathology in the processes responsible for maintenance of LTP. The

term “maintenance” is used here to denote the continued expression of tetanus-induced potentiation over a 60-min period and the mechanisms involved in this maintenance may or may not be shared by mechanisms responsible for hours- or weeks-long potentiation. The mechanisms of the trauma-induced disturbance in maintenance remain unknown. Of all cellular processes implicated in LTP maintenance, the most widely studied involves protein kinases. Protein kinase C (PKC) has been implicated in the maintenance phase of LTP. More recent evidence, however, indicates that PKC most likely is involved in mechanisms of both LTP induction and maintenance, depending on the concentration of post-synaptically injected agents [32]. For up to 3 h after FP injury, PKC activity is increased in rat hippocampus [33]. The extent to which PKC activity is perturbed chronically following TBI remains unknown, but protein kinase activity remains a suitable candidate for mediating the effects of injury on synaptic plasticity. AMPA receptor function has been implicated in the expression of LTP. Theta-burst-induced LTP is associated with increased radioimmunolabeling of phosphorylated AMPA receptors in hippocampal slices which is increased over baseline at 15 and 60 min after tetanus but not at 5 min [1]. The effects of TBI on AMPA receptor number and function largely are unknown. One study reported a lack of effect of FP injury on labeling of AMPA receptors [20], but no study has been made of AMPA conductance or kinetics following injury. Dopaminergic and glutamatergic systems have been implicated in the maintenance of LTP. D_1 -deficient mice show normal LTP initiation but poor LTP maintenance 140 min after tetanus [18]. Metabotropic glutamate receptor antagonists cause decremental fEPSP at about 1 h after tetanus [2]. The effects of TBI on chronic metabotropic receptor function are unknown but abnormal metabotropic transmission has been reported in hippocampus 15 days after FP injury [5]. Finally, calcium homeostasis has been proven crucial for LTP maintenance [14] and FP injury has been shown to result in abnormal calcium flux for as long as 4 days after injury [9]. Again, no study has been made of the chronic effects of traumatic injury on calcium but calcium homeostasis is an obvious candidate for trauma's effect on synaptic plasticity.

Ultimately, studies of hippocampal plasticity after injury must give consideration to the complex nature of the hippocampal circuit. The CA1 response is not a simple two-neuron phenomenon but is modulated by other neurons. Evidence indicates that changes in inhibitory responses follow tetanic stimulation and that such changes contribute to LTP. GABA conductances and GABA-mediated dendritic inhibitory post-synaptic potentials in CA1 cells are decreased significantly after tetanic stimulation in hippocampal slices [29]. Some evidence exists for altered inhibition in the hippocampi of injured animals [23]. Future studies should focus on the effects of trauma on inhibitory interneurons of the hippocampus and their role in any circuit dysfunction following injury.

Traumatic injury results in chemical processes that mimic those of the LTP cascade. Some investigators have speculated that such processes could result in occlusion of further synaptic plasticity [26]. The present results are inconsistent with this hypothesis. First, saturation of plasticity would have been expected to impact negatively on the induction of LTP and not selectively on the maintenance of LTP. Second, pre-potentiation or saturation by the traumatic event would have been expected to alter the initial I/O curves. I/O series in this study revealed no effect of trauma in the acute or chronic periods. Of course, the mechanisms underlying the chronic disturbance of LTP may be different from those underlying acute disturbances. Short-term fluxes in glutamate and potassium may be responsible for the failure of LTP initiation in the acute post-traumatic phase. Other disturbances, perhaps in calcium trafficking or protein kinases, could underlie the present effect in which trauma chronically affects maintenance of LTP. Clearly, the neurochemical events triggered by TBI include some of those involved in synaptic plasticity but the effect of trauma on synaptic plasticity is not simply one of occlusion or saturation.

Within the first week after surgery, slices from both injured and control animals showed modest potentiation that declined significantly across the 60 min of testing. The decline in potentiation was not different among groups. The lack of a significant difference between injured and sham animals in synaptic plasticity 6 days after surgery is surprising. At 8 weeks after surgery, sham slices supported significantly greater LTP than sham slices at 1 week after injury (t -test, $p < 0.05$) and showed no impairments in maintenance. Therefore, the sham surgery itself may be associated with reduced plasticity in the acute period. This result is consistent with a recent investigation of hippocampal plasticity in injured animals that revealed a significant depression of plasticity 24–48 h following sham surgery [4]. The authors of that report attribute the loss of plasticity to anesthetic and surgical procedures.

The results of the present study have bearing on the search for synaptic correlates of behavioral deficits. In our model, analysis of learning and synaptic plasticity on the level of the individual animal revealed no correlation between LTP and behavior. Clearly, the search for the physiological underpinnings of trauma-induced cognitive deficits continues. Disturbances in plasticity of other elements of hippocampal circuitry have not been examined after TBI. In addition, disturbances in extra-hippocampal structures likely contribute to behavioral deficits. Physiological assessment of such structures should be made in the future.

Acknowledgements

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