Electrophysiological Abnormalities in Both Axotomized and Nonaxotomized Pyramidal Neurons following Mild Traumatic Brain Injury

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Mild traumatic brain injury (mTBI) often produces lasting detrimental effects on cognitive processes. The mechanisms underlying neurological abnormalities have not been fully identified, in part due to the diffuse pathology underlying mTBI. Here we employ a mouse model of mTBI that allows for identification of both axotomized and intact neurons in the living cortical slice via neuronal expression of yellow fluorescent protein. Both axotomized and intact neurons recorded within injured cortex are healthy with a normal resting membrane potential, time constant (τ), and input resistance (R_{in}). In control cortex, 25% of cells show an intrinsically bursting action potential (AP) firing pattern, and the rest respond to injected depolarizing current with a regular-spiking pattern. At 2 d postinjury, intrinsic bursting activity is lost within the intact population. The AP amplitude is increased and afterhyperpolarization duration decreased in axotomized neurons at 1 and 2 d postinjury. In contrast, intact neurons also show these changes at 1 d, but recover by 2 d postinjury. Two measures suggest an initial decrease in excitability in axotomized neurons followed by an increase in excitability within intact neurons. The rheobase is significantly increased in axotomized neurons at 1 d postinjury. The slope of the plot of AP frequency versus injected current is larger for intact neurons at 2 d postinjury. Together, these results demonstrate that intact and axotomized neurons are both affected by mTBI, resulting in different changes in neuronal excitability that may contribute to network dysfunction following TBI.

Introduction

Traumatic brain injury (TBI), even when mild, often has long-lasting neurological consequences (Sterr et al., 2006; Levin et al., 2008; Vanderploeg et al., 2009; Blyth and Bazarian, 2010). These can include slowing of cognitive processes, confusion, chronic headache, posttraumatic stress disorder, and depression. Patients may have difficulty with even simple cognitive tasks months to years postinjury (Cicerone, 1996; Mangels et al., 2002). Confusion and slowing of brain processes are likely due to alterations in the function and connectivity of neocortical neurons, making this a critical area of investigation (Lipton et al., 2008).

The substrates associated with traumatically induced circuit dysfunction may reside in diffuse axonal injury (DAI), wherein traumatically injured axons can manifest dysfunction and/or undergo local axonal perturbation, leading to local axonal failure and disconnection. This premise has been partially supported by modern imaging studies that detect changes in fractional anisotropy within the cerebral white matter (Sharp and Ham, 2011), with the assumption that this constitutes the imaging signature of DAI. To better understand the neurophysiological consequences of traumatically induced circuit disruption and its associated axonal damage and dysfunction, various animal models ranging from axonal transection to mechanical TBI have been used. Complicating this issue is the fact that physical transection does not replicate the progressive axonal failure described with TBI (Povlishock, 1992). Further, many of the currently used animal models of TBI frequently evoke focal destructive lesions involving contusion that significantly complicates the evaluation of generalized neuronal alteration and/or circuit disruption (Povlishock and Katz, 2005). Recently, we developed a well controlled model of mild TBI (mTBI), uncomplicated by contusion and/or hematoma formation. Using this model with yellow fluorescent protein (YFP)-expressing mice, we generated DAI within the neocortex, allowing for the structural assessment of both axotomized and intact/nonaxotomized neurons (Greer et al., 2011). In the current study, we use the same model, now using slice preparations to assess the physiological status of both neuronal populations to better understand the electrophysiological consequences of mTBI.

Commercially available *Thy1-YFP-H* mice were maintained and mTBI was induced at 7–8 weeks of age via central fluid percussion injury (1.7 ± 0.04 atmospheres) by releasing a pendulum onto a fluid-filled piston to induce a brief fluid pressure pulse upon the intact dura, as previously

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Figure 1. Identification of axotomized and intact YFP⁺ layer V pyramidal neurons. **A–C**, Axotomy both proximally (**A**) and more distally (**B**, **C**) could be identified by the axon swellings (yellow arrows) in the live slice before patch-clamp recordings. Two focus levels of same image are seen in **B**. **D–I**, YFP⁺ neurons were filled with biocytin during whole-cell patch-clamp recordings 1 d postinjury (**D–G**) or in uninjured control slices (**H**, **I**). Biocytin was reacted with Texas-Red avidin (**D**). YFP expression was separately visualized (**E**). The recorded cells were confirmed as YFP⁺ with the overlap image of YFP and biocytin (**F**). Note that in **E** and **F**, a second YFP⁺ neuron that was not recorded or filled with biocytin can be seen below the recorded cell (white arrowhead). For neurons from injured brains, intact axons were observed descending to the white matter (**G**). This axon could additionally be followed for some distance in white matter perpendicular to pia (though not seen completely in this frame). Neurons from control brain sections also had axons that could be followed to the white matter (**H**, **I**). Scale bars: **A–C** (in **C**): 5 μ m (**A**), 3 μ m (**B**, **C**); **D–I** (in **D**): 20 μ m (**D–F**), 40 μ m (**G**), 51 μ m (**H**), 73 μ m (**I**).

described (Greer et al., 2011). Sham-injured animals received the same surgeries, without injury. The control cell group consisted of 10, 6, and 4 cells from naive, 2 d postsurgery shams, and 1 d postsurgery shams, respectively. There were no significant differences between controls and shams on any of 45 measures of intrinsic properties, whether both shams were considered as one group (*t* tests) or when the two sham survival groups were considered separately (one-way ANOVA). One or two days postsurgery (or at the matched age in naive mice), male mice were anesthetized with isoflurane, perfused with a cold sucrose slicing solution, and then coronally sectioned (250–300 μ m). All *in vitro* and whole-cell patch-clamp methods were performed as previously described (George and Jacobs, 2011). Whole-cell patch-clamp recordings were made from YFP⁺ layer V pyramidal neurons of somatosensory cortex whose axon could be seen either to end in an axonal swelling (axotomized) or descend into the white matter (intact). To evaluate intrinsic properties, a series of hyperpolarizing and depolarizing currents (400 ms long square step pulse at 0.3 Hz, 10–50 pA step) was applied. To confirm the firing pattern and obtain multiple sweeps for averaging of hyperpolarizing pulses, this series was repeated two to three times. Calculations were made in Clampfit (Molecular Devices), MiniAnalysis (Synaptosoft), and Excel (Microsoft).

Calculation of parameters were as follows. The resting membrane potential (RMP) was the intercept of the fit to the plot of current versus voltage at the middle of the 400 ms current step for all nonspiking sweeps. Input resistance (R_{in}) was the slope of the fit to the same plot and time constant (τ) was calculated from an exponential fit to the charging of the membrane at the onset of the largest hyperpolarization step. Action potential (AP) amplitude was measured from the first AP in the first sweep with three (or more) APs. Afterhyperpolarization (AHP) was measured from the first AHP in the first sweep with five or more APs and AHP

duration was the time from the change (decrease) in slope of the voltage after the AP (onset of AHP) to the onset of the fast rise in slope for the next AP. Rheobase was the smallest current to produce an AP and spike threshold was the interpolated membrane potential at which the first derivative of the membrane potential crossed the threshold of 10 V/s. Other parameters were calculated as previously described (George and Jacobs, 2011). Data are reported as mean $\pm$ SEM. Significance was tested using one-way ANOVAs, with least-significant difference *post hoc* tests (SPSS software), unless otherwise stated.

Results

Using differential interference contrast optics, we assessed YFP⁺ neurons, including somata and axonal appendages. Consistent with our previous report in mTBI, scattered axons revealed focal swelling and disconnection, whereas adjacent axons remained intact, revealing no abnormality (Fig. 1A–C) (Greer et al., 2011). Additional confirmation of either axonal integrity or disconnection was achieved via the use of biocytin in the recording pipette (Fig. 1D–H). The electrophysiological findings in our control population targeting YFP⁺ neocortical neurons were consistent with previous observations in YFP-H mice (Sugino et al., 2006; Yu et al., 2008), whereby regular-spiking (RS), nonadapting neurons constituted the majority of YFP⁺ neurons (Fig. 2). Neurons with two APs at much higher frequency at the beginning of the current pulse compared with the frequency of the following APs were termed doublet-RS (Fig. 2B). We divided the RS neurons into doublet and non-doublet groups to compare the percentage of cell types and for all analyses that involved the first AHP or the

Figure 2. Most YFP⁺ neurons were nonadapting RS pyramidal neurons. **A**, RS neurons were similar to those previously described. **B**, Some RS neurons had an initial doublet of action potentials, followed by nonadapting, single action potentials. **A**, **B**, Insets (dashed boxes), Single or double action potentials at the beginning of sweep at half-height double-width, as that shown in **A** and **B**. **C**, A small percentage of YFP⁺ neurons were of the previously described intrinsically bursting type. DAPs (arrowheads) were present in all groups, shown for control (**1**) and in two different cells of the intact, 2-d-survival group (**2**, **3**). **E**, Intact neurons recorded 2 d postinjury only produced single action potentials. $N = 20$ control, 10 1-d-axotomized, 8 1-d-intact, 7 2-d-axotomized, and 6 2-d-intact neurons. The scale bars in **C** apply to **A–C**; the scale bars in **D** apply only to **D**.

second AP (only non-doublet RS cells were used). The RS neurons often had a depolarizing after-potential (DAP; Fig. 2D). In addition to the RS cell types, we also found a small percentage of YFP⁺ neurons to be of the intrinsically bursting (IB) type (Fig. 2C) (Connors and Gutnick, 1990).

Following mTBI, the percentage of the different electrophysiological neuronal types described did not vary in the axotomized population (Fig. 2D). In contrast, for intact neurons, only non-doublet RS cells were found at 2 d post-TBI, with a concomitant significant decrease in the percentage of IB cells (z test, $p < 0.05$). For 1-d-intact neurons, the percentages for electrophysiological groups were similar to control values. In the few IB neurons from mTBI slices, the length and morphology of the burst was also qualitatively similar to controls.

Paralleling the loss of bursting behavior, a number of intrinsic neuronal properties were also altered in injured RS neurons. The AP amplitude was increased in axotomized YFP⁺ neurons at both 1 and 2 d postinjury (ANOVA, $p < 0.05$; Fig. 3A,B). In intact YFP⁺ neurons, the amplitude was increased at 1 d but recovered by 2 d postinjury (Fig. 3B). When the overshoot of the AP was measured, similar results were obtained (Table 1). Shown are the measurements for the first AP in the sweep; similar results were obtained for the second AP in the sweep. Since AP amplitude changes suggest Na⁺ channel alterations in injured neurons, we also examined AP rise time and threshold. These measures were not different from controls in any of the injured groups (Table 1). The AP half-width was unaffected. The AHP was significantly shortened in the same groups that showed an increase in AP amplitude (ANOVA, $p < 0.05$; Fig. 3C). Other measures of the AHP, such as peak amplitude, mean amplitude, time to peak, and rise slope, were unaffected by TBI. Early, late,

Figure 3. Intrinsic membrane properties are altered in RS neurons after mTBI. **A**, **C**, The AP amplitude was increased in 1- and 2-d-axotomized and 1-d-intact neurons. Lower dashed line in **A** indicates -60 mV RMP, middle dashed line indicates 0 mV, and upper dashed line identifies the peak for the control cell. **B**, **D**, The AHP was decreased in these same groups. $N = 15$ control, 9 1-d-axotomized, 6 1-d-intact, 6 2-d-axotomized, and 6 2-d-intact neurons. During depolarizing current steps, intact neurons from injured brains tended to fire at increased frequencies relative to control cells (**E**, examples from individual neurons, colors are the same as shown in **A**). **F**, The 2-d-intact group had a significantly steeper slope of the plot of frequency versus injected current relative to controls. **G**, The 1-d-axotomized neurons had a significantly higher rheobase compared with controls. *ANOVA, with least-significant difference *post hoc*, $p < 0.05$. # t test, $p < 0.05$.

and total adaptation were similar in control and experimental groups.

Measures of intrinsic excitability were also altered after injury (Fig. 3D–F). For axotomized neurons, the slope of the frequency-current ($F-I$) plot showed a nonsignificant trend toward a decrease at 1 d postinjury that recovered by 2 d (Fig. 3E). The 1-d-axotomized group was also significantly decreased relative to the 2-d-axotomized group (t test, $p < 0.0005$). For 2-d-intact neurons, a significant increase occurred in the $F-I$ slope relative to controls (ANOVA, $p < 0.05$; Fig. 3E). Similar results were obtained for the slope of the plot of primary frequency versus current. A significant negative correlation existed between AHP duration and $F-I$ slope for 2-d-intact group ($r = -0.92$), suggesting that these measures may be related. Other groups did not show this correlation. Although there was a trend toward an increase in R_{in} for the 2-d-intact group, no correlation existed between this measure and $F-I$ slope. The lack of correlation between these measures was true for controls and all experimental groups.

Table 1. Intrinsic properties of injured and control YFP-labeled pyramidal neurons

Measure	Control	Axotomized, 1 d	Intact, 1 d	Axotomized, 2 d	Intact, 2 d
RMP (mV)	−60.1 ± 0.3 (23)	−61.1 ± 0.8 (11)	−59.7 ± 0.3 (8)	−60.4 ± 0.7 (7)	−59.7 ± 0.4 (6)
Overshoot (mV)	50.4 ± 1.7	57.3 ± 0.9	58.2 ± 2.4	56.9 ± 1.5	48.7 ± 4.2
τ (ms)	17.1 ± 1.5	15.1 ± 1.1	15.6 ± 3.0	15.9 ± 1.5	15.1 ± 1.2
R_{in} (M Ω)	87.2 ± 7.2	87.4 ± 16.5	106.9 ± 22.2	106.5 ± 6.8	119.6 ± 6.3
Calculations for RS cells only					
RMP (mV)	−60.2 ± 0.4 (15)	−61.2 ± 0.9 (9)	−59.7 ± 0.3 (7)	−60.3 ± 0.8 (6)	−59.7 ± 0.4 (6)
τ (ms)	15.7 ± 0.9	15.6 ± 1.2	16.6 ± 3.3	15.4 ± 1.7	15.1 ± 1.2
R_{in} (M Ω)	86.4 ± 8.6	87.5 ± 20.4	116.5 ± 23.2	106.6 ± 8.1	119.6 ± 6.3
AP rise time (ms)	0.25 ± 0.02	0.28 ± 0.04	0.26 ± 0.02	0.29 ± 0.05	0.26 ± 0.02
AP threshold (mV)	−37.6 ± 0.9	−38.2 ± 0.8	−37.3 ± 0.7	−33.1 ± 1.5	−35.8 ± 1.4

Results reported as mean ± SEM (n cells).

The 1-d-axotomized group showed a transient increase in the rheobase relative to controls (one-way ANOVA, $p < 0.05$; Fig. 3F). Rheobase was unaffected in the intact groups.

Discussion

These findings are important from several perspectives. By demonstrating that these neurons are physiologically healthy, they extend previous observations (Singleton et al., 2002; Greer et al., 2011) that mTBI uncomplicated by contusion can evoke neocortical DAI that does not cause neuronal death. Equally important is the observation that within the neocortex, the same injury elicits electrophysiological change in intact neurons that is associated with increased excitability. The ultimate significance of these physiological observations remains to be determined; however, the occurrence of these posttraumatic physiological abnormalities and their persistence over 2 d alters the contemporary appreciation of mTBI, which has been assumed to evoke little brain change other than isolated/scattered axonal damage. Measures of excitability, including the $F-I$ slope and the rheobase, suggest that axotomized neurons are initially depressed, yet recover some normal properties by 2 d postinjury.

Axotomized population

Axotomy has long been known to produce changes in multiple intrinsic membrane properties (Eccles et al., 1958; for review, see Titmus and Faber, 1990), but which properties are affected depends on the type of cell, age at time of injury, and survival age (Laiwand et al., 1988; Tseng and Prince, 1996; Abdulla and Smith, 2001). For axotomized neurons in the current study, AP amplitude was increased while the AHP duration decreased at both survival times. Similar effects have been previously observed at longer survival times after transection of spinal or sympathetic neurons (Gordon et al., 1987; Yamuy et al., 1992). Previous studies of neocortical neurons after transection at the white matter or within the spinal cord, however, did not show these effects (Prince and Tseng, 1993; Tseng and Prince, 1996), suggesting that method of injury may alter outcome. It is unknown whether the *in vitro* slice preparation creates physiological abnormalities, but the difference here between injured and control is robust and would be difficult to obtain *in vivo*.

Increased number or density of Na^+ channels could account for increased AP amplitude. Such a change would be expected to decrease spike threshold and/or increase the rate of AP rise, neither of which were found in our study. Conceivably, decreases in K^+ currents could be responsible for both observations, although no significant correlation was found between these measures for any group. This result, combined with the opposing effect of an increased rheobase, suggests that several different underlying K^+ channels may be affected. Though changes in the Na^+/K^+ AT-

Pase pump have been demonstrated for short survival times after injury (Tavalin et al., 1997; Ross and Soltesz, 2000), these changes result in a depolarized RMP, a phenomenon not observed in this study, suggesting that alterations in Na^+/K^+ ATPase pump are not responsible for changes to AP amplitude and AHP duration following mTBI.

Intact population

The fact that the initial effect of mTBI on intrinsic properties of the intact population is similar to that in the axotomized neurons suggests that local activity or ion or neurotransmitter concentrations play a role in modifying the underlying currents. The intact population may have an increased capacity for recovery however, since AP amplitude and AHP duration are similar to control only 1 d later. This is further underscored by the increase in excitability appearing at 2 d postinjury, as measured by the $F-I$ slope. Similar to these findings, Topolnik and colleagues (2003) found that the $F-I$ slope in intact neurons (distant from the site of transection) was significantly greater than in axotomized cells, although neither was significantly different from control. Increases in $F-I$ slope have typically been attributed to increases in R_{in} (Gustafsson, 1979; Laiwand et al., 1988; Prince and Tseng, 1993). Surprisingly, we saw neither a significant change in R_{in} relative to controls nor a correlation between R_{in} and $F-I$ slope for any groups. Although the group showing the largest increase in $F-I$ slope did not show a significant decrease in AHP duration, there was a significant correlation of these two measures only in the intact 2-d-survival group. Thus, slight changes in R_{in} and AHP duration may make some contribution to the increased $F-I$ slope for intact neurons at 2 d survival.

To our knowledge, ours is the first report of a decrease in intrinsic bursting phenotype in a model of disease, although decreased numbers have been observed in a genetic model of neocortical malformation (Sancini et al., 2001). Intrinsic bursting behavior has been linked to an active depolarizing after-potential and underlying persistent Na^+ current (Azouz et al., 1996; Brumberg et al., 2000; Nishimura et al., 2001) and can be modified by A-type K^+ currents (Guatteo et al., 1996). A decrease in other types of bursting behavior, most similar to our doublet-RS cells, has been observed within a population of axotomized neurons (Tseng and Prince, 1996; Mentis et al., 2007). This is quite different from our results in which there is no alteration in the proportion of IB or RS neurons in the axotomized population but a reduction in intrinsic bursting activity specific to the intact population. Decreased bursting has been attributed to DAP loss (Tseng and Prince, 1996), which is altered following axotomy of lower motor neurons (Gustafsson, 1979; Takata et al., 1980), suggesting the underlying current is highly susceptible to modification after injury. In our data, although less prominent, DAPs

were present in neurons from the intact 2-d-survival group, suggesting DAP attenuation is not responsible for the loss of intrinsic bursting following mTBI.

These alterations in intrinsic bursting activity in addition to the previously discussed changes in AP amplitude and AHP duration suggest effects on Na^+ and K^+ channels. Some forms of bursting are due to a ping-pong mechanism whereby the first AP in the soma activates persistent Na^+ channels in the dendrites, producing a subsequent dendritic AP (Wang, 1999; Williams and Stuart, 1999). It is possible that changes in dendritic Na^+ and/or Ca^{2+} channels contribute to the loss of bursting observed here. After peripheral nerve injury, changes in expression levels of both sodium and potassium channels have been reported (Waxman et al., 1994; Cummins and Waxman, 1997; Ishikawa et al., 1999; Navarro, 2009; Wang et al., 2011). Less well studied are effects on central neurons, but recent reports suggest that axon stretch can induce sodium channel dysfunction and altered expression at injury thresholds below those producing axon swelling (Yuen et al., 2009). Critically, recent reports demonstrate that pharmacological blockade of voltage-gated sodium channels specific to the first node of Ranvier inhibits bursting activity within layer V pyramidal neurons (Kole, 2011). This suggests the potential for subtle axonal injury, specific to channel alteration at the initial node. Independent of morphological swelling, this may underlie the loss of intrinsic bursting activity observed within morphologically intact neurons at 2 d postinjury. The potential for trauma-induced loss of intrinsic bursting has important implications for altered neuronal networks and circuitry following mTBI. Altered functional connectivity of neocortical networks has been demonstrated following TBI and has thus far been linked to DAI (Bonnelle et al., 2011), though clinically diagnosed mTBI can occur with no detectable white matter abnormalities (Kasahara et al., 2010; Mac Donald et al., 2011). Not yet determined is the contribution of more subtle axonal change, with resultant modification of neuronal firing patterns. In light of the current findings, such a role should not be discounted and warrants further investigation.

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