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Reduced Motor Neuron Excitability is an Important Contributor to Weakness in a Rat Model of Sepsis

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Title: Reduced motor neuron excitability is the primary cause of weakness in a rat model of sepsis

Running head: Reduced motor neuron excitability

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ABSTRACT

The mechanisms by which sepsis triggers intensive care unit acquired weakness (ICUAW) remain unclear. We previously identified difficulty with motor unit recruitment in patients as a novel contributor to ICUAW. To study the mechanism underlying poor recruitment of motor units we used the rat cecal ligation and puncture model of sepsis. We identified striking dysfunction of alpha motor neurons during repetitive firing. Firing was more erratic, and often intermittent. Our data raised the possibility that reduced excitability of motor neurons was a significant contributor to weakness induced by sepsis. In this study we quantified the contribution of reduced motor neuron excitability and compared its magnitude to the contributions of myopathy, neuropathy and failure of neuromuscular transmission. We injected constant depolarizing current pulses (5 sec) into the soma of alpha motor neurons in the lumbosacral spinal cord of anesthetized rats to trigger repetitive firing. In response to constant depolarization, motor neurons in untreated control rats fired at steady and continuous firing rates and generated smooth and sustained tetanic motor unit force as expected. In contrast, following induction of sepsis, motor neurons were often unable to sustain firing throughout the 5s current injection such that force production was reduced. Even when firing, motor neurons from septic rats fired erratically and discontinuously, leading to irregular production of motor unit force. Both fast and slow type motor neurons had similar disruption of excitability. We followed rats after recovery from sepsis to determine the time course of resolution of the defect in motor neuron excitability. By one week, rats appeared to have recovered from sepsis as they had no piloerection and walked normally. However, the defects in motor neuron repetitive firing were still striking at 2 weeks and, although improved, were present at one month. To assess whether additional contributions from myopathy, neuropathy and defects in neuromuscular transmission contributed to the reduction in force generation, we measured whole-muscle force production in response to electrical stimulation of the muscle nerve. We found no abnormality in force
generation that would suggest the presence of myopathy, neuropathy or defective neuromuscular transmission. These data suggest disruption of repetitive firing of motor neurons is the primary cause of weakness induced by sepsis in rats and raise the possibility that reduced motor neuron excitability contributes to disability that persists after resolution of sepsis.

Key words: ICU acquired weakness, motoneuron, muscle, nerve, neuromuscular junction, critical illness, myopathy, neuropathy, sepsis, motor unit
INTRODUCTION

The syndrome of profound weakness following critical illness is termed ICU acquired weakness (ICUAW) and greatly complicates patient recovery. The current view is that the primary causes of ICUAW are neuropathy and myopathy (for review see (Friedrich, et al., 2015, Khan, et al., 2008, Latronico and Bolton, 2011, Stevens, et al., 2009)). However, during a prospective EMG study of ICUAW we identified a number of patients in which myopathy and neuropathy appeared insufficient to explain their severe weakness (Khan, et al., 2006). EMG records taken during voluntary contractions demonstrated that these patients had trouble recruiting motor units (Nardelli, et al., 2013). The findings raised the possibility that there might be a defect in the central nervous system that contributes to weakness.

Reduction in excitability due to sepsis has been reported in skeletal muscle, peripheral nerve and the heart (Koesters, et al., 2014, Novak, et al., 2009, Rich, et al., 1997, Rich, et al., 2002, Rossignol, et al., 2007). We wished to determine whether there might also be reduction of excitability in the central nervous system that contributes to the difficulty in recruiting motor units. In the rat cecal ligation and puncture model of sepsis, we examined motor neuron excitability by microelectrode injection of depolarizing current into spinal motor neurons in vivo. We identified a novel form of reduced motor neuron excitability that is only expressed during repetitive firing (Nardelli, et al., 2013). Our findings identified a defect in mechanisms specific to central portions of motor neurons that encode repetitive firing, thereby suggesting that reduced motor neuron excitability may contribute to weakness in patients.

In the current study we used the same rat model of sepsis to assess the relative contributions to weakness of reduced excitability of motor neurons, myopathy, neuropathy, and failure of neuromuscular transmission. Results of the present study suggest that prolonged reduction of motor neuron excitability, rather than myopathy or neuropathy, is the primary cause of weakness. We propose that difficulty with normal recruitment of motor units arising from
reduced motor neuronal excitability within the central nervous system is a major contributor to motor difficulties in patients with ICUAW.
MATERIALS AND METHODS

Ethical Approval

All procedures involving rats were approved by the Wright State IACUC committee and followed the NIH guide for care and use of laboratory animals.

Induction of sepsis

We used the cecal ligation and puncture procedure to induce sepsis in rats, which we used previously (Nardelli, et al., 2013, Novak, et al., 2009). Briefly, rats were anesthetized for survival surgery with inhaled isoflurane (1-3 % mixed in 100% O₂) and the anterior abdomen was shaved, cleaned and incised. The cecum was ligated half way between its tip and the ileum, and punctured with an 18 gauge needle. For continuous relief of pain an Alzet 2 mL osmotic pump (Durect, Cupertino CA) that delivered 30 ug/kg/hr of oxymorphone was inserted into the abdomen prior to closing the incision. At the end of surgery rats were given a single dose of buprenorphine (.12 mg/kg) subcutaneously for pain relief until the oxymorphone took effect. All rats were given 5 mls of subcutaneous 0.9% sodium chloride 24 hours after surgery. If rats appeared lethargic on postoperative days 2, 3 and 4, they were given daily additional injections of 5 mls of saline. If rats were so lethargic that they had little response to handling they were also given 10 mg/kg subcutaneous Baytril every 12 hours until they began to improve behaviorally (usually by 24 hours).

Terminal recordings

Rats were anesthetized in terminal experiments by inhalation of isoflurane (1.2-1.5% mixed in 100% O₂) and fixed in a rigid recording frame. In all experiments, the medial gastrocnemius (MG) muscle in the left hindlimb was partially dissected from surrounding tissue and attached through its cut tendon of insertion to a transducer for measuring force in isometric contractions (Aurora Scientific Inc, 205B-LR, Spike2 Cambridge Electronic Design (CED)).
Fine-wire electrodes were inserted into the belly of the MG muscle for recording EMG. With all muscle nerves crushed except the MG nerve, the tibial nerve was placed on a bipolar silver wire stimulating electrode. In experiments in which intracellular recording and stimulation of motor neurons was performed, dorsal laminectomy of L3-L6 was also performed.

Peripheral motor function: The efficacy of peripheral motor axons, neuromuscular junctions, and extrafusal muscle fibers in supporting muscle force generation was examined by direct electrical stimulation of the MG nerve or muscle. The MG muscle was fixed at optimal length for maximal isometric twitch force evoked by brief current pulses (0.04 ms) delivered to the tibial nerve. Whole-muscle isometric force was evoked by nerve stimulation to determine the force-frequency relation. Whole muscle force was also studied in response to electrical stimulation applied directly to the muscle through silver ball electrodes.

Central excitability of motor neurons: Defects in central excitability were tested by examining the action potentials fired by alpha motor neurons in response to suprathreshold current injected intracellularly through a micropipette (2 M K-acetate, 5-10 MΩ). In a subset of experiments, motor unit force was recorded simultaneously with recording of intracellular action potentials.

Statistical Analysis of Data

The effect of sepsis in rats was identified by statistical comparison of treated vs. control groups. Data sampled from rats in each group was pooled and tested for group differences using nested ANOVA, which identified the effect of sepsis as well as its dependence on individual rats. For analysis of standard deviation of firing rate, a repeated measure ANOVA was used to compare data from motor neurons from septic rats to controls at each level of current injection.
RESULTS:

We previously identified reduced excitability of motor neurons within the spinal cord of rats during sepsis. To study the contribution of this defect to weakness, we used the rat cecal ligation and puncture model of sepsis (Nardelli, et al., 2013, Novak, et al., 2009). Within 20 hours of surgery, rats developed piloerection and sat hunched without moving. Of 71 rats made septic, 11 died: 6 within 1 day, 1 at 2 days and 4 at 3 days. No rats died after day 3, and by day

Figure 1: Inability of motor neurons to sustain firing contributes to weakness 1-3 days after induction of sepsis by cecal ligation and puncture.

A) Traces from a control rat show the instantaneous firing rate (top trace, the action potentials recorded intracellularly from a motor neuron in response to microelectrode current injection (middle trace), and the isometric force generated by the motor unit, i.e. muscle fibers innervated by the impaled motor neuron. During the 5 s current injection into the soma of the motor neuron, there was sustained firing at a rate near 50 Hz. This rapid firing led to fusion of force generation by the motor unit such that muscle force was near 100 mN throughout the 5 s stimulation. B) Similar records from a septic rat. At the beginning of the current injection there was rapid spiking of the motor neuron at a rate near 50 Hz. This rapid firing caused force generation by the motor unit to begin to fuse. However, after the initial burst, firing was irregular such that there the motor unit only generated brief twitches. C) The integral of force generation over the entire 5 s stimulation was reduced by close to 50% in rats 1-3 days after cecal ligation and puncture (p < .01). For comparison of muscle force generation, current injections were matched between control and septic rats at 2 nA to 5 nA above rheobase current. N = 3 control motor units and 6 motor units from septic rats. * indicates p < .01.
5 most rats appeared in no distress as judged by absence of piloerection, normal grooming and movement around their cage. By behavioral criteria we estimate that rats were most severely septic days 1-3 following cecal ligation and puncture and had largely recovered by day 5.

We impaled motor neurons in the lumbosacral spinal cord of living, anesthetized rats, identified ones that innervated the medial gastrocnemius muscle and stimulated them to fire with a 5 s depolarizing current pulse delivered to the cell soma. At the same time we measured force production by the motor unit innervated by the impaled motor neuron. One to three days after induction of sepsis, the mean force produced during the 5s stimulation was reduced by close to 50% in motor neurons from septic rats (p < .01, Fig 1). Reduced excitability of motor neurons was a major contributor to the reduction in force. Motor neurons in control rats fired action potentials at a steady rate throughout the 5 s period of stimulation such that muscle force

![Figure 2: Sepsis induces unpredictable pauses in motor neuron firing.](image)

A) Shown is a plot of current injection exceeding rheobase versus the duration of firing for a control motor neuron and a septic motor neuron. In the control motor neuron, once the current injected was more than 3 nA above rheobase, firing was sustained throughout the 5 s current injection in every trial. The motor neuron from the septic rat often fired for less than 3 of 5 seconds, even when current was more than 5 nA above rheobase. B) Shown are 2 sequential stimulations of the same motor neuron with identical current 2 days after induction of sepsis. In the first trial, the motor neuron fired very few spikes. In the second trial the motor neuron has one pause in firing, but then fired well for the last 2 seconds of the stimulation. In C are shown 2 more trials from the same motor neuron as in B. In the top trial more current was injected than in the bottom trial, yet the motor neuron fired fewer spikes.
was sustained. In motor neurons from septic rats, firing was usually irregular such that muscle force often dropped during the 5 s stimulation. These data confirmed our previous finding of reduced motor neuron excitability and demonstrate that the defect in motor neuron excitability contributes significantly to weakness 1-3 days after induction of sepsis. (Nardelli, et al., 2013)

The defect in motor neuron excitability disrupted motor function in two ways. The first was reduction in accumulated (or total) force production. The primary cause of reduction in force was inability of motor neurons to sustain firing throughout the 5 s stimulation. In motor neurons from control rats, once current injection was 3 nA or more above rheobase current, motor neurons sustained firing throughout the 5s period of stimulation. In motor neurons from septic rats, there were pauses of up to several seconds in firing, during which force production dropped to zero (Fig 2). Increasing current injection did not eliminate pausing. The pauses were variable from trial to trial in the same motor neuron such that force production was relatively normal during one trial, only to be followed by a trial in which there was a prolonged pause and force production was greatly reduced (Fig 2). We were unable to identify any history dependence of the pauses in firing and thus were unable to predict its occurrence.

The second way that motor function was disrupted was an increase in the variability of the firing rate of motor neurons. We quantitated the increased variability using standard deviation of the firing rate. The increase in standard deviation was present at all times that motor neurons were firing (Fig 3) and was present at all levels of current injection. The increase in variability of motor neuron firing was translated into an increase in variability of force production. Thus motor neuron firing was unpredictable both on the time scale of seconds (due to pausing) and on the time scale of ms (variable firing rate). Variability in both total and moment to moment force production would be expected to substantially impair effective generation of muscle force.
Preferential atrophy of type II muscle fibers is a hallmark of the myopathy occurring in patients with ICU acquired weakness (Friedrich, et al., 2015). Type II fibers are innervated by fast motor neurons such that one potential explanation for selective atrophy of type II muscle fibers would be a selective vulnerability of fast motor neurons to sepsis-induced reduction in excitability. We categorized motor neurons by the duration of their after hyperpolarization (AHP) into fast and slow types. Motor neurons with AHP half duration < 12 ms were classified as fast and those with AHP half duration > 12 ms were classified as slow (Bakels and Kernell, 1993).

There was no difference in the mean number of spikes during a 5 s stimulus or the standard deviation of firing rate between fast and slow motor neurons in septic rats (Fig 4). These data suggest sepsis triggers a similar reduction in excitability in fast and slow motor neurons.

We followed the time course of recovery of motor neuron excitability and were surprised to find that despite apparent behavioral improvement by day 5, the defect in motor neuron firing...
was maximal 2 weeks after induction of sepsis. The number of spikes fired during the 5s stimulation was still reduced at the 1 month time point for intermediate levels of current injection. The variability of firing rate was also maximal 2 weeks after induction of sepsis and was still present at 1 month (Fig 5). These data suggest that defects in motor neuron excitability persist for weeks after resolution of sepsis.

In normal motor neurons, increasing depolarization is translated into increased firing rate (rate modulation) such that motor unit force is increased (Kernell, 2006, Powers and Binder, 2001). When the total number of spikes during a 5s period of stimulation was plotted for motor neurons from septic rats, there was no increase in the number of spikes with increased current injection 1-3 days and 2 weeks after induction of sepsis (Fig 5E). The simplest explanation would be that rate modulation was absent. However, the normal relationship between motor neuron depolarization and the instantaneous firing frequency was preserved in motor neurons from septic rats such that during periods when motor neurons were spiking, rate modulation was present at all time points studied (data not shown).
and total number of spikes was that as current injection was increased, pausing remained the
primary determinant of firing such that the total number of spikes throughout the 5s injection did

Figure 6: Lack of neuropathy, myopathy and failure of neuromuscular transmission following induction of sepsis.

A) Shown are representative examples of isometric force generated by medial gastrocnemius muscles following single and repetitive stimulation of the tibial nerve in a control and a septic rat 2 days after cecal ligation and puncture. Similar twitch and tetanic force are generated by the muscle in the septic rat. B) Shown are the EMG signal and muscle force generated during a 1 s stimulation of the tibial nerve at 20 Hz in a rat 2 days after cecal ligation and puncture. No decrement in either EMG signal or force is present. C) Plotted is the mean muscle force generated following supra-maximal stimulation of the tibial nerve at various times after induction of sepsis. No reduction is present at any time point following induction of sepsis. D) Shown is a plot of the force-frequency relationship at various times after induction of sepsis. As stimulus frequency was increased, force generation was increased due to fusion of force generation by muscle. There was increased force production at low rates of stimulation by muscle 2 days after cecal ligation and puncture. At 2 weeks force production partially returned to normal and by 1 month the plot is indistinguishable from control. For C and D, n = 4 controls, 4 two day rats, 5 two week rats, 5 one month rats.
Myopathy, neuropathy and failure of neuromuscular transmission could all contribute to the reduction in motor unit force generation after induction of sepsis. To determine the contribution of defects in the peripheral nervous system, we measured medial gastrocnemius muscle force generation in response to single and repetitive stimulation of the tibial nerve. Two days after cecal ligation and puncture, there was no evidence of myopathy or neuropathy as single stimuli to muscle yielded similar force generation in control and septic rats (Fig 6). There was also no evidence of a defect in neuromuscular transmission as there was no decrement of EMG signal or force generation during trains of pulses delivered to the tibial nerve at rates of 10 to 50 Hz (Fig 6). The stimulation frequency required for full fusion of muscle force production was shifted to lower frequencies 2 days after cecal ligation and puncture. However this shift would tend to increase force production rather decrease it. These data suggest there is no defect in the peripheral nervous system that contributes significantly to weakness during the acute phase of sepsis in rats. We conclude that during the acute phase of sepsis, weakness can be entirely accounted for by reduction in motor neuron excitability.

We followed rats for up to 1 month after cecal ligation and puncture. There was no evidence of myopathy or neuropathy at the two week and one month time points. There was an increase in muscle force generation at the two week and one month time points \( (p < .05, \text{Fig 6}) \) that was likely due to an increase in muscle mass (increased by close to 20% at 1 month). At no time during the study was there a decrement in force production during 50 Hz stimulation to suggest a defect in neuromuscular transmission (data not shown). We conclude there are no defects in the peripheral nervous system that contribute to weakness at any time point studied.
DISCUSSION

Using the rat cecal ligation and puncture model of sepsis, we found a reduction in motor neuron excitability that was responsible for a 50% reduction in force generation. Myopathy, neuropathy and failure of neuromuscular transmission were not significant contributors to the reduction in force generation. Reduction in motor neuron excitability was induced rapidly after onset of sepsis and remained reduced for weeks after apparent recovery from sepsis. We conclude reduced motor neuron excitability is the primary cause of weakness in septic rats and the defect persists for a significant period after recovery from sepsis.

Motor disability due to reduced excitability of motor neurons

We studied the firing pattern of motor neurons to injected current in vivo and were surprised to find severe deficits at times more than one week after rats appeared to have recovered from sepsis. It is important to note that our assessment of recovery from sepsis was based on gross motor behavior and did not include assessment of strength. Our recordings from motor neurons suggest that a more detailed behavioral analysis of motor function would likely pick up motor deficits in rats following sepsis.

Lower motor neurons are the final common pathway through which the CNS encodes gradations of muscle force. We found three distinct problems in the firing of lower motor neurons that would be expected to cause poor motor performance. They were: 1) reduction in number of spikes fired by motor neurons, 2) increased variability of firing rate and 3) inability to increase the number of spikes by increasing motor neuron depolarization. Each of these defects would be expected to worsen motor disability.

The easiest of these to understand is the reduction in the number of action potentials fired by motor neurons in septic rats during a 5 s stimulation. Reduction in firing of motor neurons resulted in a close to 50% reduction in force generation what would manifest as weakness. Weakness will obviously lead to reduced motor performance.
However, generation of force is not sufficient to produce the coordinated movement necessary to accomplish motor tasks. Coordinated movement requires predictable force generation by muscle. This predictability will necessarily be compromised in septic rats as there is an increase in the variability of motor neuron firing rate as measured by standard deviation of firing rate. With variable firing of motor units, force generation by muscle becomes unpredictable as motor units are the building block used to generate muscle force. The central nervous system cannot bypass the deficit in alpha motor neurons to modulate muscle force production in a predictable manner to accomplish motor tasks.

Production of coordinated movement also requires the ability to modulate the firing rate of motor units to modulate force production. The transformation of synaptic (and injected) current into firing rate is performed by lower motor neurons (Kernell, 2006, Powers and Binder, 2001). The greater the current, the greater the firing rate and the greater the force production. We found that the normal increase in number of spikes fired with increased current injection was absent in the first two weeks following induction of sepsis. However, this reduction was not due to disruption of the normal relationship between motor neuron depolarization and instantaneous firing rate. Rather, increased current injection caused greater pausing such that mean firing rate did not increase despite an increase in instantaneous firing rate during periods of motor neuron firing. Thus, following sepsis greater descending drive from the cortex will not result in the normal increase in mean firing rate of lower motor neurons to increase force generation.

Taken together our data thus suggest that while sepsis triggers weakness, the disability induced will be greater than one might expect for the degree of weakness. To normalize motor function, it will be necessary to do more than simply increase firing. It will also be necessary to lessen variability in firing rate and restore the normal relationship between the degree of synaptic input to the motor neuron and the mean firing rate.

The role of reduced motor neuron excitability in ICUAW
It was recently reported that that a single injection of bacterial lipopolysaccharide into healthy humans to acutely simulate sepsis produced mild, acute weakness of voluntary contraction, without weakness of stimulated muscle contraction. The weakness was induced within hours of the injection. The authors concluded, “Loss of volition may be a more important factor than intrinsic dysfunction in acute sepsis-associated human muscle weakness“ (McNicol, et al., 2010). Our findings provide a potential explanation for the findings as they raise the possibility that the defect “of volition” is due to reduced excitability of lower motor neurons.

The earliest we examined motor neuron excitability was one day after cecal ligation and puncture and at that early time point the defect in repetitive firing was already severe. These data suggest that inability of motor neurons to sustain repetitive firing is rapidly induced after onset of sepsis. The rapid induction of reduced excitability has implications for efforts to prevent ICUAW. Current efforts to prevent ICUAW are aimed at preventing inactivity of the motor system by mobilizing patients early in the course of sepsis. Unfortunately, our data suggest reduction in motor neuron excitability happens so rapidly, that it may occur faster than efforts to mobilize patients can be implemented. Once a motor neuron has reduced excitability, efforts to activate it during exercise will meet with limited success.

One important contributor to development of critical illness myopathy is the complete mechanical silencing of muscle that accompanies muscle inactivity in patients in the ICU (Friedrich, et al., 2015, Llano-Diez, et al., 2012, Ochala, et al., 2011). Our data suggest reduced motor neuron excitability could be an important contributor to loss of motor unit activity and mechanical silencing. It could thus contribute to subsequent development of critical illness myopathy. This could complicate recovery from ICUAW as it would mean that even after motor neuron excitability has recovered, force generation by the motor unit could remained decreased due to myopathy that developed during the prolonged period of reduced motor neuron excitability.
Lack of understanding of mechanisms causing weakness following critical illness has meant the only reliable therapy available for patients is supportive care. Non-specific treatments are applied in hopes of promoting long-term recovery of neuromuscular function, including tight glycemic control (van den Berghe, et al., 2001) and physical therapy during critical illness (Truong, et al., 2009). The discovery of a defect in motor neuron excitability raises the possibility that specific therapy could be developed. Further studies into the mechanisms underlying the reduction in excitability are under way.

Lack of myopathy and neuropathy

Clinical studies suggest sepsis is a risk factor for both neuropathy and myopathy in patients (Friedrich, et al., 2015, Latronico and Bolton, 2011). We did not find evidence of either neuropathy or myopathy in this study. One reason for the difference may be that patients with sepsis are sicker and have sepsis longer than rats following cecal ligation and puncture. Although close to 15% of the rats in our study died, rats received only fluid resuscitation and antibiotics. No rats died after day 3 and most rats appeared to have recovered within 5 days. Patients with severe sepsis are intubated, receive advanced life support and spend prolonged periods in the ICU.

However, differences in the duration and severity of sepsis cannot entirely explain the lack of myopathy or neuropathy in our study. In previous studies using the rat cecal ligation and puncture model of sepsis, both sensory neuropathy and reduction in compound muscle action potential amplitudes were found (Cankayali, et al., 2007, Novak, et al., 2009). Furthermore, there is rapid breakdown of myofibrillar proteins in rats following induction of sepsis by the cecal ligation and puncture (Hasselgren, et al., 1989, Hasselgren, et al., 1986, Williams, et al., 1999). These data strongly suggest that sepsis leads to development of myopathy and neuropathy. One reason for the lack of myopathy and neuropathy in our study may be that sample size was small such that only major contributors to weakness could be detected. Despite the relatively
small sample size, we detected a significant loss of muscle force generation due to reduction in motor neuron excitability. 

Muscle function was not entirely normal in our study. There was a lower frequency of nerve stimulation required to cause fusion of force generation. One potential explanation of these data is that there is elevation of intracellular Ca in skeletal muscle following induction of sepsis. It has been suggested that elevation of intracellular Ca during sepsis initiates the process of muscle protein breakdown that results in myopathy (Fischer, et al., 2001, Williams, et al., 1999). It may be that if the duration of sepsis was increased, myopathy would have been induced.

CONCLUSIONS:

Results presented here suggest that reduced motor neuron excitability is the primary cause of weakness in a rat model of sepsis. The reduction in excitability occurred soon after induction of sepsis and was still present weeks after sepsis had resolved. Determining the mechanism underlying this newly identified contributor to weakness may lead to novel therapy for ICUAW.

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