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ORIGINAL PAPER

Dysregulation of sodium channel gating in critical illness myopathy

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Abstract Critical illness myopathy (CIM) is the most common caused of acquired weakness in critically ill patients. While atrophy of muscle fibers causes weakness, the primary cause of acute weakness is loss of muscle excitability. Studies in an animal model of CIM suggest that both depolarization of the resting potential and a hyperpolarized shift in the voltage dependence of sodium channel gating combine to cause inexcitability. In active adult skeletal muscle the only sodium channel isoform expressed is Nav1.4. In the animal model of CIM the Nav1.5 sodium channel isoform is upregulated, but the majority of sodium current is still carried by Nav1.4 sodium channels. Experiments using toxins to selectively bock the Nav1.4 isoform demonstrated that the cause of the hyperpolarized shift in sodium channel inactivation is a hyperpolarized shift in inactivation of the Nav1.4 isoform. These data suggest that CIM represents a new type of ion channel disease in which altered gating of sodium channels is due to improper regulation of the channels rather than mutation of channels or changes in isoform expression. The hypothesis that dysregulation of sodium channel gating underlies inexcitability of skeletal muscle in CIM raises the possibility that there maybe dysregulation of sodium channel gating in other tissues in critically ill patients. We propose that there is a syndrome of reduced electrical excitability in critically ill patients that affects skeletal muscle, peripheral nerve, the heart and central nervous system. This syndrome manifests as CIM, critical illness polyneuropathy, reduced cardiac contractility and septic encephalopathy.

Keywords Action potential · Skeletal muscle · Weakness · Sepsis · Resting potential · Inactivation

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Introduction

Critical illness myopathy (CIM) was first described following co-administration of steroids and neuromuscular blocking agents (MacFarlane and Rosenthal 1977). It has subsequently been recognized that acute muscle weakness appearing in the setting of critical illness is a relatively common entity (Lacomis et al. 2000). Although CIM was first recognized in patients treated with corticosteroids and neuromuscular blockade, it is now appreciated that this is the most common cause of weakness in all patients in the intensive care unit (Lacomis et al. 1996, 1998). The development of CIM leads to increased morbidity and mortality. Patients often require prolonged ventilatory support secondary to pulmonary muscle weakness and do not regain full strength for months after their acute illness (De Jonghe et al. 2002; Herridge et al. 2003). It has recently been found that prolonged neuromuscular sequalae following critical illness is the major cause of disability in patients who survive acute respiratory distress syndrome (Herridge et al. 2003; Hudson and Lee 2003).

There are at least three factors that contribute to weakness in patients with CIM. The first is atrophy of muscle fibers and the second is loss of myosin (Lacomis et al. 1996; Larsson et al. 2000). Atrophy and loss of myosin both cause weakness due to loss of force generation following muscle fiber action potentials and might thus be considered as causing problems in excitation contraction coupling. The third factor is loss of the ability of muscle fibers to generate action potentials, which is the focus of this review. Although this review is focused on loss of muscle fiber excitability, atrophy and loss of myosin are likely more important in chronic weakness of patients with CIM whereas loss of muscle excitability may be more important in the acute setting. For review of causes of muscle atrophy and loss of myosin in patients with CIM see (Bolton 2005; Friedrich 2006).

Muscle becomes electrically inexcitable in CIM

Nerve conduction studies in patients with critical illness and weakness often reveal diminished compound muscle action potential (CMAP) amplitudes and EMG reveals scattered spontaneous activity (Bird and Rich 2002). This pattern of electrodiagnostic abnormalities is usually associated with neuropathy and thus contributed to confusion about whether the primary pathologic process was neuropathy or myopathy in critically ill patients. Critically ill patients recover from weakness over a number of weeks to months, during which time the compound muscle action potential returns to normal. This was interpreted as being due to rapid recovery from neuropathy. However, pathology of muscle and nerve in critically ill patients with weakness usually show abnormalities of muscle fibers including atrophy and loss of myosin ATPase staining; only a subset of patients have abnormalities of nerve (Lacomis et al. 1996; Latronico et al. 1996). These findings suggested that in fact most critically ill patients with weakness have myopathy rather than neuropathy. However the defects on muscle biopsy are not as severe as would be expected in patients with complete paralysis (Rich et al. 1996). The puzzling lack of correlation between the severe weakness of patients and the relative lack of pathologic changes was resolved when it was found that muscle was electrically inexcitable during periods of severe weakness in critically ill patients (Rich et al. 1996, 1997; Trojaborg et al. 2001; Bednarik et al. 2003).

An animal model of CIM has been established in rats that closely mimics the situation in patients (Rouleau et al. 1987; Massa et al. 1992). In this model the muscles in one leg are denervated by cutting the sciatic nerve. This mimics the loss of muscle activity

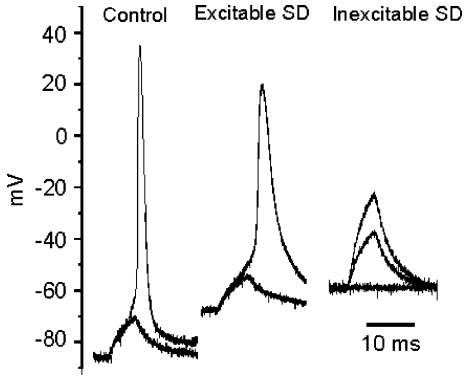

Fig. 1 Some SD muscle fibers are electrically inexcitable. Shown are traces from control, an excitable SD fiber and an inexcitable SD fiber. In each case several superimposed traces are shown. The control fiber traces are shown on the left and the SD fiber traces are shown on the right. In both control and excitable SD fibers an action potential is triggered by a relatively small depolarization. In the inexcitable fiber no action potential is present despite depolarization to –20 mV during the largest current pulse. The resting potential for the control fiber was –85 mV, the excitable SD fiber was –67 mV and the inexcitable SD fiber was –60 mV

that occurs when patients are put on neuromuscular blocking agents. Then, like many patients, the rats are given 7–10 days of high dose corticosteroids. Steroid-treated, denervated rat muscle (SD muscle) has the same histopathologic loss of myosin ATPase staining that is seen in muscle biopsy specimens from patients with CIM (Massa et al. 1992) and individual muscle fibers become electrically inexcitable (Rich et al. 1998) (Fig. 1). While the animal model of CIM does not involve any circulating factors, it has been found that serum from patients with CIM can cause changes in muscle excitability (Friedrich et al., 2004, 2005). This finding suggests there may be a contribution of circulating factor(s) to loss of muscle excitability in CIM.

Muscle inexcitability is caused by abnormal gating of sodium channels

In the rat model of CIM it was possible to study the etiology of the loss of electrical excitability in detail. Three possible mechanisms for electrical inexcitability were hypothesized: (1) The resting potential might become so depolarized that sodium channels become inactivated and unable to participate in action potential initiation. This is the mechanism underlying periods of muscle inexcitability in periodic paralysis. (2) The specific membrane resistance might become so low that action potentials cannot be initiated. (3) There might be a problem with either the number or gating of sodium or potassium channels that participate in action potentials.

Studying the role of resting potential, specific membrane resistance, and ion channels in loss of muscle excitability in rat SD muscle is complicated by several factors. First, it is necessity to combine two treatments to cause muscle inexcitability since either denervation alone or steroid treatment alone does not cause loss of excitability in a large number of fibers. However, each treatment alone causes a number of changes in muscle properties. For example denervation causes a close to 20 mV depolarization of the resting potential (Albuquerque and McIsaac 1970; Sellin and Thesleff 1980). Despite the large reduction of resting potential, the vast majority of denervated muscle fibers retain excitability (Rich et al. 1998). A second complication is that not all SD fibers become electrically inexcitable. We dealt with these complications by classifying SD fibers as either excitable (having an action potential) or inexcitable (lacking an action potential) based on their response to injection of depolarizing current. We then compared the properties between excitable and inexcitable SD fibers as well as denervated non-steroid treated and innervated steroid treated muscle. We found that inexcitable SD fibers had a mean resting potential of –61.5 ± 0.8 mV versus a mean resting potential of –67.3 ± 2.0 mV in excitable SD fibers. The additional membrane depolarization of inexcitable SD fibers is an important contributor to inexcitability. Surprisingly, despite years of research on muscle, the mechanism underlying the 20 mV depolarization of muscle upon denervation is unknown. Understanding this mechanism would be valuable in developing treatments of CIM.

Studying the role of membrane resistance in muscle fiber inexcitablility in SD muscle is also complex. Denervation of muscle causes a marked increase in specific membrane resistance of muscle (Lorkovic and Tomanek 1977; Rich et al. 1998). This increase in membrane resistance tends to increase excitability and may partially offset reductions in excitability caused by denervation-induced depolarization of the resting potential. When specific membrane resistance of SD muscle was estimated by examining the membrane time constant (assuming no change in specific membrane capacitance), it was found that it was increased relative to control (Rich et al. 1998). Thus reduction in specific membrane resistance does not contribute to inexcitability of affected SD muscle. This left an abnormality in voltage gated sodium or potassium channels as the sole remaining explanation of loss of excitability of SD muscle.

To measure voltage gated sodium and potassium currents in SD muscle we used the loose patch technique. This technique has been used extensively to study sodium currents in muscle acutely removed from the animal (Ruff et al. 1987; Ruff and Lennon 1998). We used loose patch to ask whether loss of sodium channels from the muscle membrane might underlie inexcitability. We found that when all inactivation was removed there was little difference in sodium channel density between excitable and inexcitable SD fibers (Rich and Pinter 2001). There was, however, a close to two-fold reduction in sodium channel density in both excitable SD and inexcitable SD fibers relative to control. Thus loss of sodium channels from the muscle membrane contributes to reduced excitability of SD muscle, but is not unique to inexcitable fibers.

We next examined whether a shift in the voltage dependence of sodium channel gating contributed to inexcitability of SD fibers. In excitable SD fibers we found no shift in the voltage dependence of either sodium channel activation or fast inactivation relative to control. In inexcitable fibers, however, we found a 13 mV hyperpolarized shift in the voltage dependence of both activation and fast inactivation (Rich and Pinter, 2001, 2003) (Fig. 2). The hyperpolarized shift in fast inactivation combined with the depolarized resting potential present in inexcitable SD fibers contributed to inactivation of more than 98% of sodium channels in inexcitable SD fibers. Thus fast inactivation of sodium

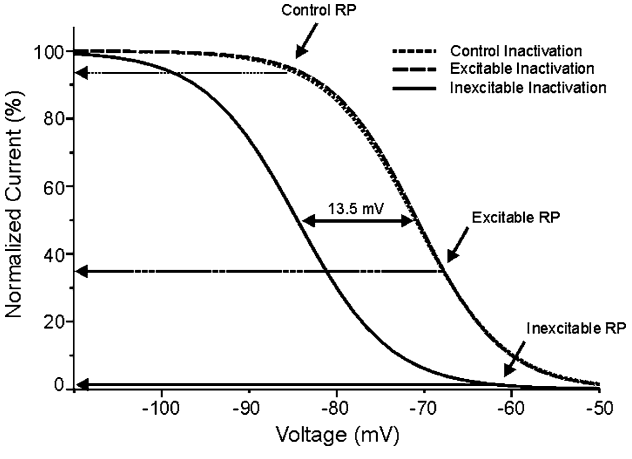

Fig. 2 The average voltage dependence of sodium channel inactivation is shifted towards hyperpolarized potentials in inexcitable SD fibers. Shown are the steady-state inactivation curves for innervated control fibers, excitable SD fibers and inexcitable SD fibers. The curves for control and excitable SD fibers are nearly superimposed. The curve for inexcitable fibers is shifted by 13.5 mV towards more negative potentials. On each inactivation curve an arrow points to the mean resting potential (RP) with a second horizontal arrow drawn to show what percent of current remains at that potential. At the mean resting potential (RP) the amount of sodium current inactivated in each group of fibers can be calculated: 9% in control fibers, 64% in excitable SD fibers, and 98% in inexcitable SD fibers

channels is the primary reason for inexcitability of affected SD fibers.

There are two ways in which the voltage dependence of sodium channel inactivation might be altered in SD fibers. The first is via expression of different sodium channel isoforms which inactivate at more hyperpolarized potentials. The second is alteration of the voltage dependence of inactivation of a given sodium channel isoform. In innervated mature skeletal muscle only the Nav1.4 sodium channel isoform is expressed. Following denervation or steroid treatment, however, there is upregulation of the Nav1.5 isoform (Yang et al. 1991; Rich et al. 1999). Normally the Nav1.5 isoform is expressed in embryonic skeletal muscle, but is downregulated during development (Yang et al. 1993). In experiments done in vitro it has been found that the Nav1.5 isoform activates and inactivates at potentials 15–20 mV more hyperpolarized than Nav1.4 (Wang et al. 1996; Zhang et al. 1999). Thus upregulation of Nav1.5 might cause a hyperpolarized shift in inactivation of the total sodium current. We examined mRNA levels of Nav1.5 in SD muscle and found marked upregulation beyond that seen in either denervated or steroid-treated muscle alone (Rich et al. 1998).

The marked increase in Nav1.5 mRNA led to the hypothesis that the Nav1.5 isoform made up the majority of sodium channels in SD muscle. To test this idea we used tetrodotoxin and u-conotoxin to selectively block sodium current carried by the Nav1.4 isoform. If upregulation of Nav1.5 was the cause of the hyperpolarized shift in the voltage dependence of inactivation, the majority of sodium current should remain after block of Nav1.4, and the remaining current should inactivate at hyperpolarized potentials. However, our data supported neither of these predictions. Despite the high levels of Nav1.5 mRNA, the majority of the current was blocked by tetrodoxin and u-conotoxin (Filatov and Rich 2004). We concluded that mRNA levels are not a good indicator of the amount of Nav1.5 in SD muscle. Furthermore, the sodium current carried by Nav1.5 did not inactivate at noticeably more hyperpolarized potentials than the sodium current prior to application of toxin. Thus despite in vitro data suggesting that Nav1.5 inactivates at more hyperpolarized potentials than Nav1.4, this may not be the case in vivo. Our findings suggested that the primary cause of inexcitability of SD fibers is a hyperpolarized shift in the voltage dependence of inactivation of Nav1.4.

CIM may represent a novel type of ion channel disease where the defect is due to neither a mutation in the channel nor a change in sodium channel isoform expression. Instead it appears to be a disease of regulation of gating of the Nav1.4 sodium channel. We do not, at this time, know the cause of the hyperpolarized shift of activation and inactivation of Nav1.4 in SD muscle. A number of in vitro studies have found that phosphorylation (Qu et al. 1994; Bendahhou et al. 1995) and glycosylation (Bennett et al. 1997; Zhang et al. 1999; Bennett 2002) can alter the voltage dependence of sodium channel gating. Future studies will be aimed at determining if defects in either phosphorylation or glycosylation underlie the abnormal gating of Nav1.4 in the animal model of CIM.

Loss of electrical excitability may affect tissues other than skeletal muscle in septic patients

What we now know about the cause of inexcitability of SD muscle has changed the way we think about critically ill patients with weakness. There are two types of patients who develop neuromuscular weakness in the ICU. In one group of patients, weakness is triggered by the combination of high dose corticosteroids and muscle inactivity (due to neuromuscular blocking agents, sedation or coma). In these patients, the acute cause of weakness is muscle inexcitability that is caused by the same factors that cause muscle inexcitability in SD fibers in rats. Clinically, these patients are awake and during nerve conduction studies, the sensory responses are normal. These patients are widely recognized to have CIM (Teener et al. 1999; Bird and Rich 2002). There is a second group of patients, however, who are weak following severe sepsis. Many of these patients have received neither high doses of corticosteroids nor neuromuscular blocking agents. Nerve conduction studies in these patients reveal reduced sensory and motor responses. These patients are usually considered to have critical illness neuropathy (CIP) (Bolton 2005). It has traditionally been thought that CIM and CIP are distinct entities that have different causes. However, more recently it has been recognized that the two syndromes often coexist (Latronico et al. 1996; Bednarik et al. 2003; Bednarik et al. 2005).

CIP and CIM could coexist for two reasons. Either they are distinct diseases that coexist in patients or they might represent different manifestations of a single underlying disorder. For example, if shifts in the voltage dependence of sodium channel inactivation occur in both nerve and muscle then they both might become inexcitable. Further, if shifts in the voltage dependence of sodium channel gating occur in multiple tissues, one would expect to see reduced excitability of all electrically active tissues in the body. This would cause a syndrome in which patients develop encephalopathy, reduced ECG amplitude, reduced sensory nerve

amplitudes and loss of muscle excitability. Is there evidence to support the existence of such a syndrome?

We previously found that skeletal muscle becomes electrically inexcitable in septic patients who have not received high dose corticosteroids or neuromuscular blocking agents (Rich et al. 1997). Some data also supports the possibility that sensory nerves become electrically inexcitable in septic patients. In a study by Latronico et al. sural nerve biopsies were performed in septic patients who had reduced sensory nerve amplitudes (Latronico et al. 1996). In a number of the biopsies, the sural nerve appeared normal despite a reduction in amplitude of the sural nerve response in that patient. There are two explanations for normal appearance of peripheral nerve in the setting of reduced nerve response amplitude. Either the reduced amplitude is due to a technical problem such as edema, or there is reduced excitability of the nerve. We found that in some patients there is a rapidly reversible reduction in sensory amplitudes that occurs in the absence of technical issues such as significant edema (Rich and Teener unpublished). We thus favor the interpretation that peripheral nerve becomes inexcitable in affected septic patients. Reversible inexcitability of nerve, as opposed to axonal loss, would explain the rapid recovery that occurs in many patients with what appears to be severe critical illness polyneuropathy.

Because cardiac tissue is electrically active, we hypothesized that the electrical activity of the heart is affected by sepsis. We reviewed ECGs from 17 patients with sepsis and found that there was a reversible reduction of ECG amplitude in patients during periods of severe sepsis (Rich et al. 2002). It did not appear that the reduction could be explained by technical issues such as pericardial effusion or pulmonary hyperinflation. The reduction in ECG amplitude we saw is very similar to the reduction we saw in 2 patients given type 1 antiarrythmic agents which block cardiac sodium channels (unpublished). This suggested to us that reduction in cardiac sodium current underlies the reduction in ECG amplitude. A reduction in cardiac sodium current might explain the reduced cardiac contractility that is seen during sepsis.

We believe available data is consistent with reduced excitability of peripheral nerve, skeletal muscle and cardiac muscle in septic patients. While there is no evidence indicating that excitability of central neurons is altered during sepsis, it is notable that many patients who have CIP also have septic encephalopathy (Bolton 2005). The pathogenesis of septic encephalopathy has never been determined. In many patients, imaging studies are normal, as would be expected if the cause were functional (i.e. electrical inexcitability) rather than structural. We have noticed that as patients recover from sepsis, septic encephalopathy improves in parallel with recovery of sensory and motor peripheral nerve amplitudes (unpublished). To us this is suggestive of a parallel recovery of electrical excitability in brain, peripheral nerve and skeletal muscle. Clearly further study is needed to determine whether the syndrome of generalized loss of excitability we propose exists in septic patients. If such a syndrome exists, it is likely that determining the mechanism underlying loss of muscle excitability in CIM will have implications for understanding dysfunction of other electrically active organs in septic patients.

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