Utilizing natural activity to dissect the pathophysiology of acute oxaliplatin-induced neuropathy

Susanna B. Park a,b, Cindy S.-Y. Lin c, Arun V. Krishnan c, David Goldstein d, Michael L. Friedlander d, Matthew C. Kiernan a,b,⁎

a Prince of Wales Clinical School, Barker Street, Randwick, Sydney, NSW 2063, Australia
b Neuroscience Research Australia, Barker Street, Randwick, Sydney, NSW 2063, Australia
c School of Medical Sciences, University of New South Wales, Barker Street, Randwick, Sydney, NSW 2063, Australia
d Department of Medical Oncology, Prince of Wales Hospital, High Street, Randwick, Sydney, NSW 2063, Australia

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A B S T R A C T

Oxaliplatin is first-line chemotherapy for colorectal cancer, but produces dose-limiting neurotoxicity. Acute neurotoxicity following infusion produces symptoms including cold-triggered fasciculations and cramps, with subsequent chronic neuropathy developing at higher cumulative doses. Axonal excitability studies were undertaken in 15 oxaliplatin-treated patients before and immediately after oxaliplatin infusion to determine whether the mechanisms underlying acute neurotoxicity altered resting membrane potential or Na+/K+ pump function. Excitability properties were assessed before and after maximal voluntary contraction (MVC) of the abductor pollicis brevis. Following oxaliplatin infusion, abnormalities developed in the recovery cycle with refractoriness markedly increased. Following activity, changes developed consistent with axonal hyperpolarization, with proportional changes pre- and post-oxaliplatin in normalized threshold. However, recovery cycle parameters following activity were significantly and disproportionally enhanced post-oxaliplatin, with partial normalization of the recovery cycle curve post-activity. Patients with the most abnormal change in the recovery cycle after infusion demonstrated the greatest changes post-contraction. Prominent abnormalities developed in Na+ channel-associated parameters in response to natural activity, without significant alteration in axonal membrane potential or Na+/K+ pump function. Findings from the present series suggest that oxaliplatin affects nerve excitability through voltage-dependent mechanisms, with specific effects mediated through axonal Na+ channel inactivation.

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Introduction

Oxaliplatin is a platinum analogue chemotherapy used extensively as first-line treatment in early stage and advanced colorectal cancer (de Gramont et al., 2000; André et al., 2004). The dose-limiting toxicity of oxaliplatin treatment is neuropathy, potentially leading to premature cessation of effective treatment and long-lasting disability. Oxaliplatin produces a unique spectrum of neuropathic symptoms, comprising acute motor and sensory symptoms which occur immediately following infusion; and chronic neuropathy which develops with increasing cumulative dose (Gamelin et al., 2002). From a motor perspective, acute oxaliplatin-induced neurotoxicity is characterized by cold-induced fasciculations and cramps affecting the distal limbs and peri-oral region, which arise during infusion and typically resolve within 3–7 days (Wilson et al., 2002; Park et al., 2008). Electrophysiological recordings have documented evidence of motor nerve hyperexcitability including high frequency repetitive discharges similar to those observed in patients with myasthenia gravis (Wilson et al., 2002; Lehly et al., 2004). Nerve excitability studies in oxaliplatin-treated patients have identified significant abnormalities arising acutely following infusion in both motor (Krishnan et al., 2005; 2006a) and sensory axons (Park et al., 2009a,b), linked to dysfunction of voltage-gated Na+ channels in the axonal membrane. Accordingly, findings from in-vitro studies have suggested that oxaliplatin may alter Na+ conductances, affecting inactivation kinetics or the voltage dependence of activation (Adelsberger et al., 2000; Grolleau et al., 2001; Webster et al., 2005; Benoit et al., 2006; Wu et al., 2009). However, the mechanisms underlying the development of an acute Na+ channelopathy in oxaliplatin-treated patients have yet to be clearly elucidated.

Axonal excitability studies have delineated the mechanisms of nerve dysfunction in a number of disorders in response to natural activity (Cappelen-Smith et al., 2000; Kuwabara et al., 2002; Krishnan and Kiernan, 2006; Krishnan et al., 2006b; Vucic et al., 2007; Krishnan...
et al., 2008). Activity alters membrane potential through activation of the Na\(^+\)/K\(^+\) pump (Vagg et al., 1998; Kiernan et al., 2004). The present study was undertaken to determine whether activity triggered generalized changes in axonal resting membrane potential or discrete changes in Na\(^+\)/K\(^+\) pump function secondary to alterations in axonal Na\(^+\) load. As such, these studies utilized the effects of natural activity to further dissect the mechanisms underlying the development of acute neuropathic symptoms in oxaliplatin-treated patients.

**Methods**

Studies were undertaken in 15 patients receiving oxaliplatin-based treatment regimens (12 males, 3 females; Table 1) referred from the Department of Medical Oncology, Prince of Wales Hospital. Participants provided written informed consent in accordance with the declaration of Helsinki and the study was approved by the South Eastern Sydney Area Health Service (Eastern Section) Human Research Ethics Committee and University of New South Wales Human Research Ethics Committee. Patients had not received prior neurotoxic chemotherapy and had no clinical or electrophysiological evidence of pre-existing neuropathy, as assessed by baseline testing. Patients received standard oxaliplatin-containing treatment regimens, with oxaliplatin (dose range 53–130 mg/m\(^2\)) administered intravenously over 2 or 6 h every 14 to 21 days (Maindrault-Goebel et al., 1999; de Gramont et al., 2000; Cassidy et al., 2004).

The present series utilized specialized threshold tracking software (© Qtrac, Institute of Neurology, UK) to control data acquisition. Stimulation was delivered using an isolated linear bipolar constant-current stimulator (DSS, Digitimer Ltd., Welwyn Garden City, UK). The median nerve was stimulated at the wrist, with a reference electrode placed 10 cm proximally. Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis (APB) muscle with the reference electrode 4 cm distal (Fig. 1A). Responses were amplified (Medelec Sapphire 4ME, Surrey, UK) with electronic noise removed (Hum Bug 50/60 Hz Noise Eliminator, Quest Scientific Instruments, North Vancouver, Canada). Temperature was monitored at the site of stimulation and maintained above 32 °C. Multiple nerve excitability parameters were assessed as reported previously (Kiernan et al., 2000) to assess axonal ion channel function and membrane potential. A stimulus–response curve was obtained by increasing the stimulus current in 2% increments until maximal compound amplitude was reached. Threshold was defined as the stimulus current (mA) required to produce a potential of a target size corresponding to the steepest slope (typically ~40% of supramaximal CMAP amplitude; Bostock et al., 1998).

Excitability properties were measured before and after maximal voluntary contraction (MVC) of the APB muscle for 60 s, during which time stimulation was not delivered, in patients both before and after oxaliplatin infusion (Vagg et al., 1998). Patients abducted the thumb against resistance provided by the same investigator in each experiment. The hand and arm were stabilized to limit movement.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (± SEM)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Single dose (mg/m(^2))</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>Cumulative dose (mg/m(^2))</td>
<td>398 ± 31</td>
</tr>
<tr>
<td>Cycle tested</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Acute symptoms (% of patients)</td>
<td>100</td>
</tr>
<tr>
<td>OSN/NCI scale (median)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 1**

Clinical characteristics of the patient cohort.

![Stimulating & Recording Apparatus](infusion_pump.png)

**Fig. 1.** (A) Clinical testing paradigm, with stimulating and recording set-up undertaken in a patient receiving intravenous chemotherapy. (B) Recording parameters during multitrack protocol to assess excitability properties before and after maximal voluntary contraction. Parameters were recorded across six channels: Ch 1) a control stimulus of 1 ms duration, Ch 2) a short stimulus of 0.2 ms duration, Ch 3) a stimulus following 100 ms of 40% of threshold depolarizing current pulse, Ch 4) a stimulus following 100 ms of 40% of threshold hyperpolarizing current pulse, Ch 5) a stimulus 5 ms following a supramaximal conditioning stimulus and, Ch 6) a supramaximal stimulus.
Changes were assessed using the multitrack protocol to provide continuous sequential assessment of excitability parameters to sequentially assess different parameters (Fig. 1B). Parameters were assessed across six channels to measure the threshold current required to produce the target potential for 1) a control stimulus of 1 ms duration, 2) a short stimulus of 0.2 ms duration, 3) a stimulus following a conditioning stimulus of 100 ms of 40% of threshold depolarizing current pulse, 4) a stimulus following a conditioning stimulus of 100 ms of 40% of threshold hyperpolarizing current pulse, 5) a stimulus 5 ms following a supramaximal conditioning stimulus and, 6) a supramaximal stimulus.

Strength–duration time constant, an indirect marker of persistent Na\(^+\) channel activity (Mogyoros et al., 1996; Bostock and Rothwell, 1997) was calculated using the 1 and 0.2 ms width stimuli, according to Weiss' law (Weiss, 1901). Threshold electrotonus represented the changes in threshold in response to subthreshold (40% of threshold current), assessed at the completion of 100 ms current steps in both depolarizing (TEd) and hyperpolarizing (TEh) directions, to evaluate internodal function (Bostock et al., 1998). The recovery cycle of excitability following impulse conduction was assessed as the threshold change produced in response to a supramaximal stimulus followed by a conditioning stimulus at different interstimulus intervals varying from 2.5 to 200 ms (Kiernan et al., 1996, 2000).

The recovery cycle utilized a paired pulse paradigm to elucidate the pattern of changes in excitability following impulse conduction. Immediately following an impulse, the axon becomes inexcitable due to inactivation of voltage-gated Na\(^+\) channels responsible for impulse generation (Hodgkin and Huxley, 1952). This absolute refractory period is followed by a 3-ms period of reduced excitability termed the relative refractory period (Hodgkin and Huxley, 1952). This period is followed by a 3-ms period of reduced excitability termed the relative refractory period (Hodgkin and Huxley, 1952). This period may encroach on this interval, as identified in previous studies (Grosskreutz et al., 2000). For this reason, the recovery cycle at 5 ms is typically associated with the superexcitable period (Kiernan et al., 1996, 2000), large increases in excitability following impulse conduction. Repeatedly applied stimuli of the same magnitude eventually reduces the excitability following impulse conduction (Barrett and Barrett, 1982; Kiernan et al., 1996). Finally, a subexcitable phase is induced by slow K\(^+\) channel activation, before the axon returns to a baseline state (Baker et al., 1987). In the present study, recovery cycle parameters were expressed as the percentage increase in threshold required to produce the target potential at each interstimulus interval, as is conventional in previous studies (Kiernan et al., 2000). Recovery cycle parameters were reported at 2.5 ms interstimulus interval (typically associated with refractoriness; Kiernan et al., 1996, 2000), 5 ms interstimulus interval, and the minimum mean threshold change after interstimulus intervals of greater than 10 ms. Because threshold is reduced during the 5 ms interval (corresponding to the superexcitable period), it is represented as a negative value. However, although the recovery cycle at 5 ms is typically associated with the superexcitable period (Kiernan et al., 1996, 2000), large increases in the refractory period may encroach on this interval, as identified in previous studies (Grosskreutz et al., 2000). For this reason, the recovery cycle at 5 ms was chosen for assessment in the multitrack protocol because any increases in refractoriness may preclude tracking at shorter interstimulus intervals.

Clinical grading scales were utilized to determine neurotoxicity severity, including the Oxaliplatin-Specific Neurotoxicity Scale (OSNS): Grade 1—dysesthesia or paresthesia that completely regressed before the next cycle of therapy; Grade 2—dysesthesia or paresthesia persisting between courses of therapy; and Grade 3—dysesthesia or paresthesia causing functional impairment (Cassidy and Misset, 2002). In addition, the Neuropathy Sensory Subscale of the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Scale (Version 3) was utilized as follows: Grade 1 (Mild)—loss of deep tendon reflexes or paresthesia not interfering with function; Grade 2 (Moderate)—sensory alteration or paresthesia

Table 2
Acute neuropathic symptoms in the patient cohort following oxaliplatin.

<table>
<thead>
<tr>
<th>Acute neuropathic symptoms</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>93%</td>
</tr>
<tr>
<td>Cold sensitivity</td>
<td>87%</td>
</tr>
<tr>
<td>Cramps/fasciculations</td>
<td>13%</td>
</tr>
<tr>
<td>Pharyngolaryngeal dysesthesia</td>
<td>13%</td>
</tr>
<tr>
<td>Jaw pain/stiffness</td>
<td>7%</td>
</tr>
<tr>
<td>Symptom duration</td>
<td></td>
</tr>
<tr>
<td>1–2 days</td>
<td>40%</td>
</tr>
<tr>
<td>3–5 days</td>
<td>33%</td>
</tr>
<tr>
<td>&gt;6 days</td>
<td>27%</td>
</tr>
</tbody>
</table>

Fig. 2. Recovery cycle parameters compared pre-infusion (black) to post-infusion recordings (white). (A) Recovery cycle parameters at 2.5 ms were markedly increased from 31.3±6% pre-infusion to 77.5±21% post-infusion (P<.005). (B) Recovery cycle at 5 ms was reduced from −21.1±1% pre-infusion to −3.8±5% post-infusion (P<.005). (C) Recovery cycle >10 ms was increased from 15.8±1% pre-infusion to 21.2±2% post-infusion (P<.005).
interfering with function but not activities of daily living; Grade 3 (Severe)—sensory alteration or paresthesia interfering with activities of daily living; and Grade 4—disabling (Trotti et al., 2003).

Results were expressed as mean±standard error of the mean. Results pre- and post-oxaliplatin infusion treatment were grouped within patients and compared utilizing Wilcoxon sign rank tests (two-tailed). Correlations were performed using Pearson correlation coefficients. Data was collated into 1-min intervals for each patient. Each minute was normalized to baseline values (pre-activity). A normalized value of 1 indicated that no change occurred following activity compared to baseline. Following activity, a normalized value of greater than 1 indicated that the parameter increased compared to baseline. A normalized value of less than 1 indicated that the parameter decreased relative to baseline. Maximal changes across excitability parameters were compared within patients pre- and post-activity, and also pre- and post-oxaliplatin infusion using Wilcoxon sign rank tests (two-tailed). Significance was defined as P≤0.05. All statistics were performed in SPSS (Version 18, SPSS Inc., Chicago, US).

Results

Patients with colorectal cancer (Stages II–III 60%; Stage IV 40%; mean age 58±4 years) were assessed prior to a single oxaliplatin infusion and immediately following infusion (single oxaliplatin dose 86±4 mg/m²; Table 1). Patients were assessed at a median of the 4th treatment cycle (range 3–7 cycles), corresponding to a mean cumulative oxaliplatin dose of 398±31 mg/m². All patients experienced acute neuropathic symptoms, including cold-induced cramps and fasciculations in the hands and feet, which resolved within 2 to 10 days after infusion (Table 2). Most patients experienced mild neurotoxicity, with a median NCI neurotoxicity scale and OSNS scale score of 1.

Following oxaliplatin infusion, abnormalities developed in the recovery cycle of excitability as previously described (Krishnan et al., 2005, 2006a; Park et al., 2009b). The recovery cycle curve was shifted upwards, with threshold change markedly increased at 2.5 ms (Pre: 31.3±6%; Post: 77.5±21%; P<.005; Fig. 2A), reduced at 5 ms (Pre: −21.1±1%; Post: −3.8±5%; P<.005; Fig. 2B) and increased at >10 ms interstimulus intervals (Pre: 15.8±1%; Post: 21.2±2%; P<.005; Fig. 2C). The extent of abnormalities in recovery cycle parameters that developed post-infusion was significantly correlated with oxaliplatin dose (recovery cycle at 2.5 ms correlation coefficient=.794; P<.001; recovery cycle at 5 ms correlation coefficient=.778; P<.005).

Excitability changes induced by natural activity

To determine mechanisms underlying the development of acute oxaliplatin-induced nerve abnormalities, threshold measurements were recorded before and after 1 min of maximal voluntary contraction (MVC) in patients both pre- and post-oxaliplatin infusion. In all patients, changes developed consistent with axonal hyperpolarization following activity (Vagg et al., 1998). However, the change in recovery cycle parameters at 5 ms following activity was significantly enhanced post-oxaliplatin (Pre: 1.48±.1; Post: 3.9±.7; P<.05; Figs. 3A and 4A), with a greater than 2.5 fold increase as compared to pre-infusion. In contrast, there were no significant differences in the extent of threshold change pre- and post-oxaliplatin infusion (normalized threshold Pre: 1.24±.04; Post: 1.27±.07; NS; Figs. 3B and 4B), indicating that the degree of hyperpolarization was not altered post-oxaliplatin infusion and comparable to previous studies (Vagg et al., 1998; Kuwabara et al., 2001). Proportional changes before and after oxaliplatin infusion developed in threshold electrotonus (hyperpolarizing threshold electrotonus 90–100 ms Pre: 1.25±.02; Post: 1.23±.03; NS; Fig. 4C; depolarizing threshold electrotonus 90–100 ms Pre: 1.14±.02; Post: 1.16±.03; NS; Fig. 3C) and strength–duration time constant (Pre: 0.89±.02; Post: 0.88±.03; NS; Fig. 3D). There were no reductions in maximal CMAP amplitude following activity pre- or post-oxaliplatin infusion.
In a second series of studies undertaken to further investigate the effects of natural activity on excitability parameters following oxaliplatin, the recovery cycle of excitability was assessed at 17 interstimulus intervals ranging from 2.5 to 200 ms. Prior to oxaliplatin administration, changes following activity occurred in all phases consistent with axonal hyperpolarization (Fig. 5A; recovery cycle 2.5 ms Pre: 31.6±11.3%; Post: 13.7±5.6%; \( P < .05 \); recovery cycle 5 ms Pre: −19.2±1.7; Post: −25.1±1.9; \( P < .05 \); recovery cycle >10 ms Pre: 17.1±1.9; Post: 9.2±0.8%; \( P < .05 \)). Following oxaliplatin administration, the same qualitative pattern occurred but the extent of change was significantly enhanced in all phases (Fig. 5B,C). Subsequently, following 1 min of natural activity, the recovery cycle was normalized towards baseline levels during all phases (Fig. 5B,C). Subsequently, following 1 min of natural activity, the recovery cycle was normalized towards baseline levels during all phases (Fig. 5B,C). Subsequently, following 1 min of natural activity, the recovery cycle was normalized towards baseline levels during all phases (Fig. 5B,C).

Further, there were no differences in baseline threshold before or after oxaliplatin administration (Pre: 4.0±0.4 mA; Post: 3.9±0.3 mA; NS), suggesting that a generalized shift in membrane potential did not occur post-oxaliplatin infusion. In addition, Na+/K+ pump function did not appear to be affected by oxaliplatin administration, with identical rates of recovery of threshold pre- and post-oxaliplatin infusion (NS; Fig. 6A).

Patients who had the most abnormal recovery cycle parameters following oxaliplatin infusion demonstrated the greatest change post-contraction. Maximal change in recovery cycle parameters (at 5 ms) following activity was significantly correlated to baseline recovery cycle values following oxaliplatin infusion (correlation coefficient = .882; \( P < .005 \); Fig. 6B). This finding would suggest that oxaliplatin-induced abnormalities in nerve function were partially reversible with hyperpolarization in all patients, irrespective of the extent of oxaliplatin-induced dysfunction pre-contraction.

Discussion

The present study has investigated changes in axonal excitability following natural activity in oxaliplatin-treated patients in vivo to
Further define the mechanisms underlying acute neurotoxicity. Disproportionate changes were evident in recovery cycle parameters post-oxaliplatin infusion, with significantly increased abnormalities following activity. In contrast, quantitatively similar changes in threshold, strength–duration time constant and threshold electrotonus following activity were obtained before and immediately after oxaliplatin infusion, arguing against generalized changes in axonal membrane potential or specific Na+/K+ pump dysfunction post-oxaliplatin infusion. The hyperpolarization induced by natural activity was sufficient to partially rectify abnormalities in oxaliplatin-treated patients following a single infusion, suggesting that oxaliplatin-induced nerve abnormalities were responsive to changes in membrane potential.

Activity-dependent changes in membrane potential

Following conduction of a long train of impulses, a hyperpolarizing afterpotential develops (Gasser, 1935; Bergmans, 1968). The accumulation of Na+ ions intracellularly following impulse generation leads to over-activity of the electrogenic Na+–K+ pump (Bostock and Graft, 1985; Morita et al., 1993), producing an accumulation of negative charge inside the axon and consequently membrane hyperpolarization (Rakowski et al., 1989). The effects of activity have been utilized to study axonal function in normal nerves and in a variety of disease states (Kiernan et al., 1997; Cappelen-Smith et al., 2000; Kaji et al., 2000; Kuwabara et al., 2002; Krishnan and Kiernan, 2006; Krishnan et al., 2006b; Vucic et al., 2007; Krishnan et al., 2008).

Accordingly, in the present series, the pattern of change following natural activity was consistent with axonal hyperpolarization both pre- and post-oxaliplatin infusion, similar to the findings in previous studies (Bostock et al., 1998; Vagg et al., 1998; Kaji et al., 2000; Lin et al., 2000; Cappelen-Smith et al., 2000; Kuwabara et al., 2001; Kuwabara et al., 2002). However, the extent of change in the recovery cycle of excitability was disproportionately greater following oxaliplatin infusion than expected for the degree of hyperpolarization. Furthermore, oxaliplatin-induced abnormalities in Na+ channel function were partially reversible with further hyperpolarization. The mechanisms underlying changes in response to natural activity appear related to the acute effects of oxaliplatin on axonal membrane properties, as discussed below.

Mechanism of acute-oxaliplatin induced neurotoxicity

A number of studies, both clinical and in vitro, have suggested that acute oxaliplatin-induced neurotoxicity is related to dysfunction of axonal Na+ channels (Adelsberger et al., 2000; Webster et al., 2005; Krishnan et al., 2005, 2006a; Kiernan and Krishnan, 2006; Park et al., 2009a,b). In vitro studies have suggested that oxaliplatin may induce effects on Na+ channel inactivation kinetics and specifically that the voltage-dependence of inactivation becomes altered following oxaliplatin treatment (Adelsberger et al., 2000; Grolleau et al., 2001; Webster et al., 2005; Benoit et al., 2006; Wu et al., 2009). In the present study, acute abnormalities developed in motor axons immediately post-infusion (Krishnan et al., 2005, 2006a; Park et al., 2009b) with significantly increased refractoriness. Oxaliplatin administration has been demonstrated to increase the refractory period in vitro, in the absence of membrane potential changes, as determined for patients in the present study (Adelsberger et al., 2000). The refractory period is a marker of the inactivation of voltage-gated Na+ channels (Bergmans, 1968), and modulation of refractoriness has been linked to alteration of Na+ channel inactivation properties in a number of nerve disorders (Kiernan et al., 2005; Krishnan et al., 2009a,b).

Inactivation of Na+ channels represents a significant molecular target for toxin and drug activity (Ulbricht, 2005). Inactivation is voltage-dependent, with 30% of Na+ channels inactivated at resting membrane potential, with this proportion increasing with depolarization (Schwarz et al., 1995). In the present study, natural activity induced axonal hyperpolarization (Vagg et al., 1998). The hyperpolarization produced by natural activity in the present study appeared sufficient to partially rectify the proposed changes in Na+ channel function, consistent with oxaliplatin altering the voltage-dependence of Na+ channel inactivation.

The characteristic features of acute oxaliplatin neurotoxicity, including repetitive after-discharges following voluntary activity and spontaneous high frequency discharges in motor nerves (Wilson et al., 2002; Lehky et al., 2004), may produce secondary effects on neuromuscular transmission at the motor endplate. Experimental models have demonstrated enhanced neurotransmitter release from the motor nerve terminal leading to spontaneous discharges and increased frequency of discharges following a stimulus in the presence of oxaliplatin (Webster et al., 2005). However, the consequences of Na+ channel dysfunction at the distal nerve terminals may be expected to produce dramatic increases in refractoriness at short interstimulus intervals, potentially leading to conduction failure, as demonstrated in tick paralysis and acute motor axonal neuropathy (Kuwabara et al., 2001; Kuwabara et al., 2003; Krishnan et al., 2009b). The distal axon has a lower safety margin of conduction (Westerfield et al., 1978) and is not effectively protected by the blood–nerve barrier making it vulnerable to toxic insults (Olsson, 1969).

However, such changes were not observed in the present study, arguing against any distal abnormalities in acute oxaliplatin-induced neurotoxicity. Instead, hyperpolarization produced by natural activity in the post-contraction period was suf

Fig. 6. (A) To examine changes in the rate of threshold recovery due to differences in Na+/K+ pump activity, the recovery of threshold in the post-contraction period was compared between pre-oxaliplatin (black squares) and post-oxaliplatin infusion recordings (white squares), demonstrating lack of change. (B) Patients who had the most abnormal recovery cycle (5 ms) values following oxaliplatin infusion demonstrated the greatest change in recovery cycle post-contraction, with maximal change following activity significantly correlated to baseline recovery cycle values (5 ms) post-oxaliplatin infusion (Correlation = .882; P < .005).
served to normalize deficits in axonal excitability induced by oxaliplatin. Previous excitability studies have identified a different pattern of acute excitability change in sensory axons following oxaliplatin administration (Park et al., 2009a,b), qualitatively similar to the effects of the Na+ channel blocker tetrodotoxin on sensory nerves (Kiernan et al., 2005). Importantly, correlation was identified between the extent of oxaliplatin-induced abnormalities in both motor and sensory axons (Park et al., 2009b), suggesting that the factors underlying acute oxaliplatin-induced abnormalities in sensory and motor axons are likely to be related. Such abnormalities in motor axons may represent a useful biomarker of acute oxaliplatin-induced neurotoxicity, reflecting generalized peripheral nerve toxicity. With increasing numbers of patients receiving oxaliplatin as first-line treatment, the importance of clearly delineating the mechanisms underlying neurotoxicity will be intensified in order to develop successful treatment approaches. The present study has demonstrated changes in response to natural activity in oxaliplatin-treated patients in vivo in the clinical setting, establishing disproportionate changes in response to natural activity in Na+ associated parameters and suggesting that oxaliplatin produces discrete abnormalities in Na+ channel function. Acute oxaliplatin-induced changes in nerve function were membrane potential dependent and are likely to reflect specific changes in the inactivation properties of axonal Na+ channels. Taken in total, these findings provide a more discrete target for the development of therapeutic strategies, suggesting that modulation of Na+ channel inactivation properties may be of most benefit in reducing acute oxaliplatin-induced neuropathy.

References


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