Regional differences in ulnar nerve excitability may predispose to the development of entrapment neuropathy

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Objective: To assess whether there are differences in nerve excitability properties between proximal and distal stimulation sites in the ulnar nerve in healthy controls, which may provide information on whether alteration in ion channel function predisposes to the development of ulnar neuropathy at the elbow.

Methods: Nerve excitability studies were undertaken in 11 healthy controls. Studies were undertaken with stimulation of the ulnar nerve at the elbow and wrist. Recordings were obtained from abductor digiti minimi in both sets of studies.

Results: Recordings obtained following stimulation of the nerve at the elbow demonstrated significant differences to those obtained following stimulation of the nerve at the wrist. Specifically, there was a left shift in stimulus–response curves at the elbow compared to the wrist, with prolonged strength-duration time constant, and reduced rheobase (P < 0.05). These changes were accompanied by increased refractoriness and reductions in superexcitability and late subexcitability (P < 0.05).

Conclusions: The present findings may suggest relative depolarization of ulnar nerve axons at the elbow.

Significance: These changes may reflect regional differences in axonal Na+/K+ pump function and thereby predispose the ulnar nerve to conduction failure and axonal degeneration when exposed to trauma.

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1. Introduction

Entrapment of the ulnar nerve entrapment at the elbow is the second most common entrapment neuropathy. The most frequent site of entrapment is in the humeroulnar arcade, between the heads of the flexor carpi ulnaris muscle. Clinical features include paresisae affecting the medial digits IV and V, with weakness of intrinsic hand muscles developing in more severe cases. While the prognosis of ulnar neuropathy at the elbow (UNE) remains variable, persistence of symptoms and ongoing disability is evident in 40–50% of patients at 2-year follow-up (Dunselman et al., 2008; Evoli et al., 2003).

The key predisposing factor to the development of UNE relates to the superficial location of the nerve at this site (Dellon and Mackinnon, 1988). In addition to anatomical predisposition, it remains conceivable that regional differences in biophysical properties may also contribute to the development of neuropathic processes (Bae et al., 2009; Krishnan et al., 2004). For example, length-dependent gradients in biophysical properties have been postulated to contribute to the development of distal neuropathy (Krishnan et al., 2004). These differences were demonstrated through the use of nerve excitability techniques, clinical techniques that provide information about axonal ion channel properties and membrane potential (Bostock et al., 1998; Krishnan et al., 2008; Kuwabara et al., 2002; Park et al., 2009). Consequently, the present study utilized nerve excitability to investigate whether there were differences in ulnar nerve biophysical properties

Abbreviations: ADM, abductor digiti minimi; APB, abductor pollicis brevis; CMAP, compound motor action potential; FCR, flexor carpi radialis; SEM, standard error of the mean; UNE, ulnar neuropathy at the elbow.

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between proximal and distal stimulation sites that may be an additional factor underlying the development of UNE.

2. Methods

Excitability studies were undertaken on 11 healthy volunteers (3 men, 8 women; age range 24–45 years; mean age 34.2 years). None of the participants had symptoms or clinical signs of peripheral nerve dysfunction. Subjects gave informed consent to the procedures, which were approved by the Committee on Experimental Procedures Involving Human Subjects of the University of New South Wales.

Standard ulnar nerve motor conduction was assessed in all subjects to exclude subclinical neuropathy at the elbow. There was no evidence of conduction block or slowing across the elbow in any of the subjects (forearm conduction velocity: 58.2 ± 1.6 m/s; elbow conduction velocity 60.6 ± 1.3 m/s; mean ± standard error of the mean). Excitability studies were performed using an automated computerized system (Qtrac© Institute of Neurology, Queen Square, UK). The target amplitude for threshold tracking was set to 30–40% of supramaximal response amplitude, utilizing the area of steepest slope of the stimulus response curve. Changes in the threshold current required to achieve the target amplitude were tracked on-line, with the tracking steps proportional to the error between target amplitude and actual response (Bostock et al., 1998; Kiernan et al., 2000). Stimulation was computer controlled and converted to current using an isolated linear bipolar constant current stimulator (maximal output ±50 mA; DS5, Digitimer, Welwyn Garden City, UK).

In the first series of studies, the ulnar nerve was stimulated at the wrist, using non-polarizable electrodes (4620 M, Unomedical Ltd., Birkerød, Denmark), with the anode placed ~5 cm superiorly over the midline of the forearm. The resultant compound motor action potential (CMAP) was recorded from the abductor digiti minimi muscle (ADM), with the active recording electrode placed over the motor point and the reference electrode placed 4 cm distally. In the second set of studies, the ulnar nerve was stimulated at the elbow, between the olecranon and medial epicondyle, with the anode placed over the inferior part of the biceps muscle. Studies were performed with the elbow flexed. Recordings obtained from the same site, as with wrist stimulation. Responses were amplified (ICPS11 AC amplifier, Grass Technologies, West Warwick, USA) with electronic noise removed (Hum Bug 50/60 Hz Noise Eliminator, Quest Scientific Instruments, North Vancouver, Canada). Temperature was monitored with a thermistor thermometer (5831-A, Omega Engineering, Manchester, UK). Mean skin temperature was identical at both stimulation sites (elbow 33.3 ± 0.4°C; wrist 33.3 ± 0.3°C).

The following excitability indices were assessed using the TROND-CMW2 protocol: (i) Stimulus–response behavior using two stimulus durations. The ratio between the stimulus–response curves for two stimulus durations was used to calculate rheobase (two stimulus durations). The ratio between the stimulus–response behavior using two stimulus durations. The ratio between the stimulus–response behavior using two stimulus durations. The ratio between the stimulus–response behavior using two stimulus durations. The ratio between the stimulus–response behavior using two stimulus durations. The ratio between the stimulus–response behavior using two stimulus durations).

3. Results

Prominent differences in excitability parameters were identified between wrist and elbow stimulation sites (Figs. 1 and 2). Mean data established that stimulus–response curves were relatively shifted to the left at the elbow, with the mean stimulus intensity required to generate a stimulus 40% of maximal significantly lower in elbow recordings (elbow 3.4 ± 1.2 mA; wrist 5.0 ± 1.1 mA, P < 0.05). These differences were not explained by alterations in CMAP amplitude which were not significantly different between the two sites (elbow 7.4 ± 1.0 mV; wrist 7.7 ± 1.1 mV).

The changes in axonal threshold were accompanied by a longer strength-duration time constant in elbow recordings (elbow 0.49 ± 0.02 ms; wrist 0.38 ± 0.02 ms; P < 0.01; Fig. 2A), providing an indirect measure of the activity of a nodal persistent Na⁺ conductance. In addition, rheobase, defined as the threshold for a stimulus of infinitely long duration, was lower in elbow recordings (elbow 2.2 ± 1.2 mA; wrist 3.5 ± 1.1 mA, P < 0.05; Fig. 2B).

Significant differences were also noted in parameters of threshold electrotonus, reflecting the activity of internodal conductances (Fig. 1B). There was greater reduction in depolarizing threshold electrotonus at the 10–20 ms interval (elbow 60.6 ± 1.6%; wrist 66.2 ± 1.2%; P < 0.05; Fig. 2C), which was accompanied by reduced S2 accommodation (elbow 16.1 ± 1.1%; wrist 20.9 ± 1.0%, P < 0.05; Fig. 2D) and a trend towards reduced change in hyperpolarizing threshold electrotonus at the 90–100 ms interval (elbow −103.6 ± 4.3%; wrist −112.8 ± 4.3%, P = 0.13). There were no significant differences in current–threshold parameters.

Prominent differences were also noted in recovery cycle parameters between the two stimulation sites. The relative refractory period, which reflects recovery from inactivation of voltage-gated transient Na⁺ channels, was increased in elbow recordings (elbow 3.4 ± 1.0 ms; wrist 2.8 ± 1.0 ms, P = 0.001; Fig. 1C) as was refractoriness, measured as the percentage increase in threshold at an interstimulus interval of 2.5 ms (elbow 30.2 ± 3.6%; wrist 12.0 ± 1.8%, P < 0.001). Superexcitability, measured at an interstimulus interval of 5 ms, was also reduced in elbow recordings (elbow 18.0 ± 2.1%; wrist 22.6 ± 2.0%, P = 0.051) as was late subexcitability measured as the maximum mean of three adjacent points at interstimulus intervals >15 ms (elbow 6.0 ± 0.8%; wrist 12.3 ± 1.3%, P < 0.001).

4. Discussion

The present study, undertaken to explore whether biophysical differences may further predispose to the development of UNE, established significant excitability differences between elbow and wrist stimulation sites in healthy controls. Specifically, there was a leftward shift in stimulus–response curves at the elbow compared to the wrist, with prolonged strength–duration time constant and reduced rheobase. These changes were accompanied by reduced change to subthreshold polarizing currents, increased refractoriness and reductions in superexcitability and late subexcitability. Findings from the present study may suggest relative depolarization of ulnar nerve axons at the elbow, consistent with the pattern of change noted in previous studies where membrane potential was altered indirectly by ischaemia (Kiernan and Bostock, 2000).
4.1. Regional differences in peripheral nerve excitability

Previous studies, exploring regional differences in excitability properties, have demonstrated differences in excitability for recordings obtained from proximal and distal muscles innervated by the same peripheral nerve (Jankelowitz et al., 2009; Krishnan et al., 2004). Studies of excitability parameters obtained from tibialis anterior and extensor digitorum brevis following peroneal nerve stimulation at the fibular neck, demonstrated relative depolarization of recordings from tibialis anterior (Krishnan et al., 2004). A more recent study of median nerve axons (Jankelowitz et al., 2009) demonstrated that excitability parameters obtained from flexor carpi radialis (FCR) were depolarized compared to recordings obtained from abductor pollicis brevis (APB). There was however no significant difference in excitability between elbow and wrist stimulation to APB which led to the conclusion that any difference in excitability parameters was due to changes at the muscle level, such as differences in properties of the innervated motor units (Jankelowitz and Burke, 2009).

The present study differed in method from those previous studies as the simulation site was altered while the recording site was kept constant. Given that excitability recordings are local measures of nerve function that reflect biophysical properties underlying the stimulating electrode (Bostock et al., 1998), the present study...
suggests that there are differences in biophysical properties along the length of a peripheral nerve. Differences in axonal size between the elbow and wrist are unlikely to underlie these differences given that reduction in axonal diameter occurs only in close proximity to the muscle and not in the nerve trunk per se (Caruso et al., 1992; Rexed, 1944). It may be argued that differences in fascicular organisation between axons at the elbow and wrist underlie the changes noted in this study, given that fascicular organisation changes frequently throughout the course of a nerve (Stewart, 2003; Sunderland, 1990; Sunderland and Ray, 1948). However, while this may explain the differences in axonal thresholds, it is unlikely to explain the systematic changes in excitability that were recorded in the present study. This view is supported by previous excitability studies that have demonstrated that isolated changes in threshold do not cause significant differences in the excitability of motor or sensory axons (Kiernan et al., 1996).

4.2. Potential causes and clinical implications of excitability differences

The axonal Na+/K+ pump plays an important role in the maintenance of resting membrane potential. Na+/K+ pump dysfunction leads to an excess of positive charge inside the axon and contributes to the subsequent depolarisation of membrane potential (Kaji and Sumner, 1989; Ritchie and Straub, 1957). In the present study, the excitability changes noted with elbow stimulation suggest relative membrane depolarisation of axons in the proximal ulnar nerve. There are a number of possible causes for this change, including relative compression of the nerve at the elbow, physiological adaptation or a proximal–distal gradient in Na+/K+ pump function. Ulnar nerve compression at the elbow was excluded in all subjects in the present study, using standard nerve conduction studies. Physiological adaptation would be more likely to result in an increase in Na+/K+ pump activity in proximal regions of the nerve and consequent hyperpolarization, the converse of the changes noted in the present study, as a means of negating the potential depolarizing effects of compression and ischaemia. Accordingly, the differences between the two stimulation sites may potentially reflect a proximal–distal gradient in Na+/K+ pump function or distribution. The basis for this assertion is derived from previous studies that have demonstrated greater internodal lengths in the proximal regions of peripheral nerves (Caruso et al., 1992; Gassel and Trojaborg, 1964) and a nodal predominance of the Na+/K+ pump (Ariyasu et al., 1985; Wood et al., 1977). Therefore, a lower density of the Na+/K+ pump in the proximal regions of the ulnar nerve may underlie the excitability differences between elbow and wrist stimulation sites. While more proximal recordings following stimulation of the ulnar nerve in the axilla may be informative, excitability studies of this region pose technical difficulties due to the high stimulation intensities required to produce a potential and the problems with maintaining stability of stimulating electrodes (Krishnan et al., 2009).

From a clinical perspective, differences in biophysical properties may represent an additional contributing factor to the development of UNE. Extrinsic neural compression, which has long been regarded as the major cause of UNE, leads to nerve injury by inducing nerve ischaemia and/or mechanical deformation (Dahlin et al., 1984). Nerve ischaemia in turn causes impairment in energy-dependent processes, including the function of the Na+/K+ pump, leading to intracellular retention of positive charge and membrane depolarization (Rakowski et al., 1989). External compression of the ulnar nerve would therefore be expected to further exacerbate the excitability changes of relative membrane depolarization noted in elbow recordings. The consequences of axonal depolarization include the development of ectopic impulse generation leading to paraesthesiae (Mogyoros et al., 2000, 1999), a common symptom of UNE, and conduction block, a well-recognised neurophysiological abnormality (Dunselman et al., 2008), which may occur due to inactivation of nodal Na+ channels (Krishnan et al., 2008). In addition, chronic membrane depolarization may lead to reverse activation of the Na+/Ca2+ exchanger, which triggers a cascade of events that leads to axonal loss, which ultimately underlies long-term disability in UNE (Crane et al., 2004).

In conclusion, the present study has provided evidence for differences in biophysical properties between proximal and distal regions of the ulnar nerve. The findings appear to suggest relative depolarization of ulnar nerve axons at the elbow and may reflect differences in axonal Na+/K+ pump function along the course of the nerve. These differences may represent an additional contributing factor to conduction failure and axonal degeneration in UNE.

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