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Sodium-potassium pump assessment by submaximal electrical nerve stimulation

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HIGHLIGHTS

- Activity dependent hyperpolarization can be induced using submaximal stimulation.
- Submaximal stimulation was not considered painful.
- Submaximal stimulation is suitable for assessing sodium-potassium pump function.

ABSTRACT

Objective: Sodium-potassium pump dysfunction in peripheral nerve is usually assessed by determining axonal hyperpolarization following maximal voluntary contraction (MVC) or maximal electrical nerve stimulation. As MVC may be unreliable and maximal electrical stimulation too painful, we assessed if hyperpolarization can also be induced by submaximal electrical nerve stimulation.
Methods: In 8 healthy volunteers different submaximal electrical stimulus trains were given to the median nerve at the wrist, followed by 5 min assessment of thresholds for compound muscle action potentials of 20%, 40% or 60% of maximal.
Results: Threshold increase after submaximal electrical nerve stimulation was most prominent after an 8 Hz train of at least 5 min duration evoking submaximal CMAPs of 60%. It induced minimal discomfort and was not painful. Threshold increase after MVC was not significantly higher than this stimulus train.
Conclusions: Submaximal electrical stimulation evokes activity dependent hyperpolarization in healthy test subjects without causing significant discomfort.
Significance: Sodium-potassium pump function may be assessed using submaximal electrical stimulation.

1. Introduction

Excitability studies suggested that sodium-potassium pump dysfunction in peripheral nerve motor axons may contribute to the pathogenesis of diabetic neuropathy and amyotrophic lateral sclerosis (Vucic et al., 2007; Krishnan et al., 2008). In these studies pump function was assessed by determining threshold increase for motor axon excitation following maximal voluntary contraction (MVC) of a muscle innervated by those axons. This threshold increase arises because the intra-axonal sodium accumulation and potassium loss resulting from sustained nerve impulse firing is restored by temporarily increased pump activity. Because, per cycle, the pump removes 3 positive sodium-ions from the axon and puts only 2 positive potassium-ions back into the axon, its action results in a net loss of positive charge at the inside of the axolemma, giving rise to axonal hyperpolarization and threshold increase (Skou, 1957).

The use of MVC to assess pump-function in patients has, however, potential drawbacks since subjects may not fully activate their muscle, the precise firing rate in axons is unknown in a given

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; MVC, maximal voluntary contraction; SDTC, strength-duration time constant; TEd90-100, depolarizing threshold electrotonus at 90–100 ms; TEh90-100, hyperpolarizing threshold electrotonus at 90–100 ms.

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patient, and unstable or blocked impulse propagation proximal to the testing site may preclude MVC (Cappelen-Smith et al., 2000). Repetitive electrical nerve stimulation to activate the pump instead of MVC avoids these drawbacks, but using maximal electrical nerve stimuli can cause significant patient discomfort.

The present study assessed if trains of submaximal electrical nerve stimuli are tolerable and cause sufficient axonal hyperpolarization to assess pump function.

2. Methods

2.1. Subjects

We investigated 8 subjects (7 men, mean age 35 years). All subjects were healthy, except for one who had carpal tunnel syndrome. Informed consent was obtained from all subjects. The investigation was done in accordance to the Declaration of Helsinki and was approved by the local medical ethics committee.

2.2. Protocol

The right median nerve was stimulated at the wrist via non-polarizable surface electrodes (Red Dot, 3 M Health Care, Germany; cathode at the wrist; anode 10 cm proximal over the radial aspect of the forearm) and the thenar compound muscle action potential (CMAP) was recorded by surface disk electrodes of 10 mm diameter in a belly-tendon montage. The set-up consisted of: (i) a Viking IV EMG-apparatus (Nicolet Biomedical, Inc., Madison, Wisconsin) for recording thenar CMAPs and delivering stimulus trains to the median nerve at the wrist, (ii) an isolated bipolar constant current stimulator (DS5, Digitimer, UK model D185-HB4) for delivering test and conditioning stimuli at the wrist, and (iii) a computer (PCI-6221, National instruments) running QtracS software (TRONDNF, version 19-06-2015, Institute of Neurology, Queen Square, London, UK) for controlling test and conditioning stimuli. Test stimuli were 1.0 ms duration current pulses which estimated the threshold current for a CMAP of a given percentage of its maximal amplitude by means of proportional threshold tracking. Target CMAP is defined as this percentage of the maximal CMAP amplitude used for threshold tracking. To control for fatigability and other changes in the maximal CMAP amplitude, a supramaximal electrical stimulus was provided every stimulus cycle to assess the maximal CMAP amplitude at that moment.

Tests consisted of the following parts: (i) tracking baseline threshold for 1 min, (ii) delivering a stimulus train to induce a threshold change, and (iii) tracking thresholds after the stimulus train for 5 min. Train CMAP is defined as the amplitude of the CMAPs during the stimulus train as a percentage of the maximal CMAP amplitude. The train CMAPs in a stimulus train varied from 40% to 100% of the maximal CMAP. Stimuli in a train were rectangular pulses of 0.2 ms duration. Thresholds were assessed by test stimuli delivered at 2 Hz for target CMAPs of 20%, 40% or 60%. Mean threshold was calculated every 30 s. Threshold increase was normalized by defining it with respect to the mean baseline threshold. Per recording we measured normalized peak-threshold increase and normalized end-threshold increase. Per subject, each of the test paradigms was conducted on a different day. We also assessed threshold recovery after MVC or submaximal electrical nerve stimulation by calculating the recovery rate. This was defined as the mean absolute threshold change per minute over the first 3 min after MVC or submaximal electrical stimulus train.

To exclude threshold changes induced by temperature change during testing, we monitored skin temperature continuously by a temperature sensor at the wrist. For the same purpose, we also assessed distal motor latency (DML) every 1.6 s throughout each test, since changes in DML reflect changes in nerve temperature (Franssen and Wieneke, 1994).

Immediately after the test, subjects were asked to score discomfort based on a 9-point comfort scale (O'Brian et al., 2003), containing: painful (0), hurting (1), concerning pressure (2), irritant (3), constantly annoying (4), occasionally annoying (5), constantly noticeable (6), occasionally noticeable (7) and not noticeable (8).

The study consisted of 4 parts. First, a preliminary investigation was conducted in 7 subjects to assess if a threshold increase was induced by stimulus train rates of 7, 8, 10, 15, or 20 Hz and stimulus train durations of 1, 2, 5, 7, or 10 min. Next, the 4 electrical stimulation paradigms protocols yielding the most prominent threshold increases were selected from the results of the first part and systematically tested in all subjects. Then, the paradigm resulting in the largest threshold increase and the smallest discomfort was tested 3 times in every subject to assess reproducibility by means of the coefficient of variation (CoV) within each subject. CoV was defined as the standard deviation of the peak thresholds, divided by the mean of the peak thresholds. Finally, threshold increase after MVC for 1 min was compared with threshold increase after a submaximal electrical stimulus train.

We also assessed how accurately the setting for a train CMAP of 60% actually induced a CMAP of 60% of its maximal amplitude. In 3 subjects an 8 Hz stimulus train with a train CMAP of 60% was given, but instead of recording the threshold changes, the amplitude of every CMAP was recorded using the CMAP-scan application (Sleutjes et al., 2014) on another Viking EMG apparatus (Version 20.1, Natus Neurology Incorporated, Inc., Middleton, WI, USA).

To confirm that the observed threshold increase following submaximal electrical nerve stimulation indeed reflected hyperpolarization of resting membrane potential (Vagg et al., 1998), an extra excitability test was performed in 3 subjects, assessing those excitability parameters that are most sensitive to changes in membrane potential (Bostock and Bergmans, 1994; Kiernan et al., 2004; Vagg et al., 1998). Thus, the following parameters were tested before and after a stimulus train with a train CMAP 60% for 7 min: strength-duration time constant (SDTC) which is the absolute value of the x-intercept of the Qt relation (relation between stimulus charge and stimulus duration, calculated using pulses of 0.2, and 1.0 ms); hyperpolarizing threshold electrotonus 90–100 ms (TEh90-100) which is the threshold increase at the end of a 40% hyperpolarizing conditioning stimulus of 100 ms; depolarizing threshold electrotonus 90–100 ms (TEd90-100) which is the threshold decrease at the end of a 40% depolarizing conditioning stimulus of 100 ms; fanning which is the sum of the absolute values of TEd90-100 and TEh90-100; supernormality which is the decrease of the threshold 6.3 ms after a preceding supramaximal pulse.

2.3. Analysis

Statistical analysis was performed with SPSS (version 21; IBM). To assess normality we applied the Shapiro-Wilk test. Since data were not normally distributed, statistical analysis of thresholds and discomfort scores was performed by the Wilcoxon signed test. $P < 0.05$ was considered statistically significant. All data is presented as median and interquartile range (IQR) unless specified otherwise.

3. Results

3.1. Basic investigations

The preliminary investigation showed that at least 5 min of electrical nerve stimulation at a rate of 8 Hz was required to obtain