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Clinical Neurophysiology 117 (2006) 1444–1448

www.elsevier.com/locate/clinph

Distal excitability changes in motor axons in amyotrophic lateral sclerosis

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Accepted 7 April 2006

Abstract

Objective: Previous axonal excitability studies in amyotrophic lateral sclerosis (ALS) have suggested that impaired potassium channel function could be responsible for the generation of fasciculations, but the ectopic activity arises predominantly from the motor nerve terminals. This study tested the hypothesis that dysfunction of potassium channels is more pronounced in the more distal parts of axons.

Methods: Threshold electrotonus was used to compare accommodation at the motor point of abductor pollicis brevis, and at the wrist portion of the median nerve, between 22 patients with ALS and 19 normal subjects. As target responses for motor point stimulation, movement-related potentials were recorded using an accelerometer.

Results: Compared to normal subjects, ALS patients showed greater threshold changes to depolarizing conditioning currents at both the motor point and wrist, suggesting less accommodation by potassium currents. Differences in the threshold electrotonus curves between the normal and ALS groups were much more prominent at the motor point than at the wrist.

Conclusions: In ALS, axonal potassium channels are impaired more prominently in distal portions of axons than at the nerve trunk, and this is consistent with evidence that fasciculations mostly arise from the nerve terminals.

Significance: Excitability testing at the motor point provides additional information about the pathophysiology of ALS.

Keywords: Amyotrophic lateral sclerosis; Potassium channel; Motor nerve terminal; Fasciculation; Threshold tracking

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurological disease, and the mechanisms underlying the characteristic selective degeneration and death of motor neurons remain poorly understood. Fasciculation is a prominent and characteristic feature of ALS, presumably due to increased excitability of some part of the motor neuronal membrane. There is good evidence that the predominant anatomical sites of origin of fasciculations are the intramuscular motor nerve terminals (Layzer, 1994; Roth, 1982, 1984), although some fasciculations arise proximally early in the disease (Carvalho and Swash, 1998). Fasciculations may be benign, but they may also, rarely, occur before any motor neurone death, as a precursor to ALS (Carvalho and Swash, 2004; Fleet and Watson, 1986). A better understanding of their membrane mechanism may therefore provide insights into the pathophysiology of ALS.

The anatomical and biophysical characteristics of the motor nerve terminals are different from those of the nerve trunk. In the most distal part of the motor axon, sodium channels are less expressed, whereas potassium channels are expressed more than in the nerve trunk (Brigant and Mallart, 1982; Konishi, 1985; Lindgren and Moore, 1989; Mallart, 1984, 1985).

In the 1990s, the threshold tracking technique was developed to measure a number of indices of axonal excitability non-invasively in human subjects, such as threshold electrotonus, and current–threshold relationships (Bostock et al., 1998; Burke et al., 2001; Kiernan and Bostock, 2000; Kiernan et al., 2000; Kuwabara et al.,

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1388-2457/$30.00
doi:10.1016/j.clinph.2006.04.005

2000). These indices can provide an indirect insight into sodium or potassium channel functions. Bostock et al. (1995) applied the threshold electrotonus test in the ulnar nerve at the wrist of 11 ALS patients, and suggested voltage-dependent potassium channel dysfunction in ALS. On the basis of strength-duration measurements in motor and sensory axons, Mogyoros et al. (1998) suggested that persistent sodium currents may be increased. A recent study investigating the median nerve at the wrist of 58 ALS patients with multiple excitability measurements has supported both of these suggestions (Kanai et al., 2006). However, these studies examined excitability properties in the nerve trunk (the wrist portion of the median or ulnar nerve), remote from the suspected site of origin of fasciculations.

Two techniques have been described for measuring axonal excitability properties more distally than at the wrist. First, Walters et al. (2001) showed that palmar stimulation could be used for axons innervating the abductor pollicis brevis (APB) with recording compound muscle action potentials (CMAPs), then Kuwabara et al. (2004) and Trevillion et al. (2004) showed that nerve excitability could be tested successfully at the motor point, using an accelerometer or force transducer to measure muscle contraction. The accelerometer method has now been used to test whether abnormal membrane excitability is more prominent in the distal portions of motor axons in ALS patients.

2. Methods

2.1. Subjects

Experiments were performed on 22 patients who conformed to the El Escorial criteria (Brooks et al., 1994) for clinically probable or definite ALS (11 men and 11 women; ages, 54–75 years; mean, 66 years), seen at Chiba University Hospital between 2003 and 2005. Their disease duration ranged from 4 to 30 months (mean, 13 months). These patients were a separate group from the 58 studied with nerve excitability testing at the wrist only by Kanai et al. (2006). We excluded ALS patients with other neurological disorders, such as diabetic neuropathy and entrapment neuropathy, and those with acidosis due to respiratory failure. On electromyography, fasciculation potentials were present in 15 of the 22 ALS patients. Control data was obtained from 19 age-matched normal subjects (7 men and 12 women; ages, 46–80 years; mean, 61 years). All normal subjects and patients gave informed consent to the procedures, which were approved by the Ethics Committee of Chiba University School of Medicine.

2.2. Stimulation and recordings

The excitability measurement was performed by a computerized threshold tracking program (QTRAC version 4.3 with multiple excitability protocol TRONDHM; copyright, Prof. Hugh Bostock, Institute of Neurology, London, UK). Threshold tracking measures axonal excitability at the site of stimulation (Bostock et al., 1998), and we measured axonal excitability properties in the median motor nerve at the wrist and at the motor point of APB.

Two kinds of recordings were performed, and differences between normal controls and ALS patients by the same methods were, respectively, compared at the stimulation to the wrist and motor point:

(1) Electric stimulation at the ‘wrist’ with recording CMAPs.
(2) Electric stimulation at the ‘motor point’ (distal axons) with recording movement-related potentials using an accelerometer.

First, CMAPs were recorded from APB with conventional surface electrodes after electric stimulation of the median nerve at the wrist in a belly tendon fashion so that CMAP amplitude was maximal. Second, the thumb movements were recorded as the movement-related potentials using an accelerometer (SV114, NEC San-ei, Tokyo, Japan) placed at the thumb tip after electric stimulation of the median nerve at the motor point of APB (Fig. 1). The motor point was determined at the same site as active electrode for CMAP recording. For motor point stimulation, the active electrode placed over APB, and the remote electrode positioned 10 cm proximal over the

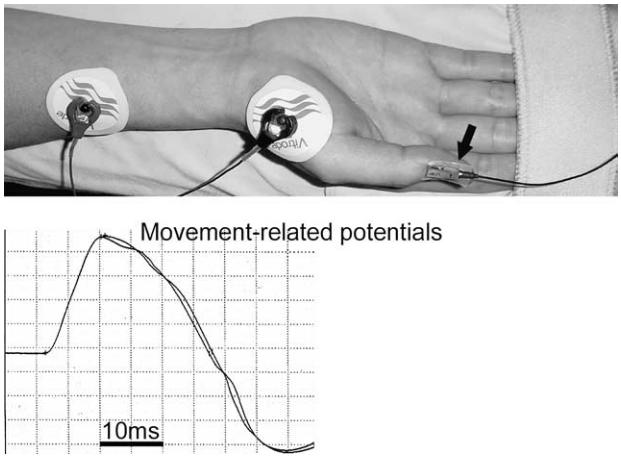

Fig. 1. Position of the accelerometer and stimulating electrodes for motor point stimulation of the abductor pollicis brevis, and raw waveforms of movement-related potentials. The sensor was placed at the tip of the thumb (arrow). The stimulus occurs at the left marginal bold line. Compound muscle action potentials were separately recorded using conventional surface electrodes.