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The effects of mexiletine on excitability properties of human median motor axons

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Abstract

Objective: To investigate the effects of mexiletine, an analog of lidocaine, on excitability of human axons in vivo.

Methods: Threshold tracking was used to measure multiple excitability indices (strength-duration time constant, rheobase, refractoriness, supernormality, and threshold electrotonus) in median motor axons of 20 patients with neuropathic pain or muscle cramping, before and 3 months after treatment with oral 300 mg mexiletine per day.

Results: After treatment, there was a reduction in pain/muscle cramps, associated with decreased strength-duration time constants ($P=0.01$), increased rheobasic currents ($P=0.06$), and lower refractoriness ($P=0.02$), all of which were consistent with reduced nodal Na^+ currents. Supernormality and threshold electrotonus did not change significantly. The changes in strength-duration properties suggest a decrease in persistent Na^+ conductance. The lowered refractoriness after treatment might result from reduced transient Na^+ currents, but the lack of change in supernormality and threshold electrotonus was not consistent with this hypothesis.

Conclusions: Oral mexiletine in a dosage of 300 mg daily suppresses persistent Na^+ currents in human motor axons.

Significance: Measurements of the excitability indices can be used for non-invasive assessment and monitoring of the effects of mexiletine in patients with neuropathic pain or muscle cramps.

Keywords: Mexiletine; Sodium channel; Persistent sodium channel; Neuropathy; Axonal excitability; Threshold tracking

1. Introduction

Mexiletine is an orally active local anesthetic agent, which is structurally related to lidocaine, and has been used for alleviating neuropathic pain (Dejgard et al., 1988; Oskarsson et al., 1997; Stracke et al., 1992), and occasionally for muscle cramp (Kanai et al., 2003). Neuropathic pain and muscle cramping partly arise from axonal hyperexcitability, which leads to abnormal spontaneous firing associated with increased Na^+ channel expression (Waxman et al., 1999). The mechanism of action of mexiletine is a blockage of Na^+ channels (Jarvis and Coukell, 1998), and this agent would decrease axonal excitability by reducing nodal Na^+ currents. However, this has rarely been demonstrated in human axons, presumably because of the lack of appropriate tools to assess axonal ionic conductances in human subjects.

In the 1990s, the threshold tracking technique was developed to measure a number of axonal excitability indices such as strength-duration properties, refractoriness, and threshold electrotonus, non-invasively in human subjects (Bostock et al., 1998; Burke et al., 2001; Kiernan et al., 2000; Kuwabara et al., 2002). These indices depend on the biophysical properties of the axonal membrane at the site of stimulation, and can provide an insight into Na^+ and K^+ conductances (Bostock et al., 1998; Burke et al., 2001). We have used this technique to investigate whether mexiletine administration is associated with specific changes in ionic conductances in human axons.

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2. Methods

2.1. Subjects

Twenty patients (8 men and 12 women), who received mexiletine treatment for neuropathic pain or severe muscle cramping, were studied (Table 1). Their age ranged from 20 to 74 years (mean 49 years). Of the 20 patients, 6 patients had painful neuropathy caused by diabetes, systemic vasculitis, alcohol abuse, or a demyelinating form of Guillain–Barré syndrome. The remaining 14 patients received mexiletine treatment for their severe muscle cramping; postulated causes of muscle cramps included spinal muscular atrophy, Machado–Joseph disease, and axonal Guillain–Barré syndrome. Three patients had no obvious neurological disease, and were diagnosed as having idiopathic muscle cramp. A part of data from patients with Machado–Joseph disease was described elsewhere (Kanai et al., 2003).

Table 1
Clinical profiles of patients treated with mexiletine

Patient	Age/sex	Diagnosis	Disability score[a]	
			Before treatment	After treatment[b]
Neuropathic pain				
1	20/F	Diabetic neuropathy	3	1
2	54/F	Vasculitic neuropathy	3	2
3	74/F	Vasculitic neuropathy	2	2
4	26/M	Guillain–Barré syndrome	2	1
5	44/M	Guillain–Barré syndrome	2	1
6	58/M	Alcoholic neuropathy	2	2
Muscle cramp				
7	25/M	Guillain–Barré syndrome	2	0
8	52/F	Spinal muscular atrophy	3	0
9	53/F	Spinal muscular atrophy	3	1
10	53/M	Machado–Joseph disease	3	0
11	65/F	Machado–Joseph disease	3	0
12	61/M	Machado–Joseph disease	3	1
13	62/M	Machado–Joseph disease	3	1
14	49/F	Machado–Joseph disease	3	0
15	62/M	Machado–Joseph disease	2	0
16	53/F	Machado–Joseph disease	2	0
17	60/F	Machado–Joseph disease	2	1
18	51/F	Idiopathic	2	1
19	52/F	Idiopathic	2	1
20	56/F	Idiopathic	3	1

[a] See the text.
[b] $P<0.01$, compared with scores before treatment.

The normal control data of excitability testing with threshold tracking were obtained from 54 healthy subjects (35 male and 19 female; aged 23–84 years; mean age 44 years). All patients and normal subjects gave informed consent to the experimental procedures, which have been approved by the Ethics Committee of the Chiba University School of Medicine.

2.2. Clinical assessment of pain/muscle cramp

A pain/cramp disability score (Kanai et al., 2003) was used to evaluate the extent of disability in performing daily activities: 0, no symptom; 1, a complaint but no disability; 2, a chief complaint, sometimes disturbing work or sleep; 3, a chief complaint, disturbing work or sleep daily. All the 20 patients included in this study had the score 2 or 3.

2.3. Excitability testing using threshold tracking

Multiple excitability measurements were performed using a protocol designed to measure rapidly a number of different nerve excitability parameters (in ~10 min), which uses a computerized program (QTRAC version 4.3 with multiple excitability protocol TRONDHM; copyright, Prof. Hugh Bostock, Institute of Neurology, London, UK) as described elsewhere (Kiernan et al., 2000; Kuwabara et al., 2002). The compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis after stimulation of the median nerve at the wrist. Skin temperature was measured near the stimulating site, and maintained above 31.5 °C. The protocol began with the measurement of stimulus response curves using test stimuli of duration 0.2 and 1.0 ms. From these curves, strength-duration time constant (SDTC) were calculated using the formula (Kanai et al., 2003; Kiernan et al., 2000):

$$\mathrm{SDTC} = 0.2(I_{0.2} - I_{1.0})/(I_{1.0} - 0.2I_{0.2})$$

where $I_{0.2}$ and $I_{1.0}$ are the respective threshold currents for test stimuli of 0.2 and 1.0 ms duration. SDTC is defined as ratio between the minimum charge threshold and the rheobase, and equates to chronaxie (Bostock et al., 1998; Burke et al., 2001).

In the following measurements, the current required to produce a CMAP that was 40% of the maximum was tracked. The recovery cycle of axonal excitability following a single supramaximal stimulus, was recorded from the test stimulation delivered at different intervals after the conditioning stimulus. The relative refractory period was determined as the time of the first intercept of the recovery cycle curve to the *X*-axis, and refractoriness was defined as the threshold increase during the relative refractory period.