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Mexiletine suppresses nodal persistent sodium currents in sensory axons of patients with neuropathic pain

Sagiri Isose [a], Sonoko Misawa [a], Kenichi Sakurai [b], Kazuaki Kanai [a], Kazumoto Shibuya [a], Yukari Sekiguchi [a], Saiko Nasu [a], Yuichi Noto [a,c], Yumi Fujimaki [a,d], Koutaro Yokote [b], Satoshi Kuwabara [a,*]

[a] Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba, Japan
[b] Department of Clinical Cell Biology and Medicine, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba, Japan
[c] Department of Neurology, Kyoto Prefectural Medical University, Kyoto, Japan
[d] Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

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ABSTRACT

Objective: To investigate changes in axonal persistent Na^+ currents in patients with neuropathic pain and the effects of mexiletine, an analogue of lidocaine, on axonal excitability properties.
Methods: The technique of latent addition was used to estimate nodal persistent Na^+ currents in superficial radial sensory axons of 17 patients with neuropathic pain/paresthesias before and after mexiletine treatment. Brief hyperpolarizing conditioning currents were delivered, and threshold change at the conditioning-test interval of 0.2 ms was measured as an indicator of the magnitude of persistent Na^+ currents.
Results: Threshold changes at 0.2 ms in latent addition were greater in the neuropathic patients than in the normal controls ($p < 0.001$). After mexiletine treatment, there was a reduction in clinical pain scores ($p < 0.001$), associated with decreased threshold changes at 0.2 ms ($p < 0.001$).
Conclusions: In patients with neuropathy, nodal persistent Na^+ currents in large sensory fibers increase, and the abnormal currents can be suppressed by mexiletine. Pain reduction after mexiletine treatment raises the possibility that excessive Na^+ currents are also suppressed in small fibers mediating neuropathic pain.
Significance: Latent addition can be used for indirect *in vivo* monitoring of nodal Na^+ currents in large sensory fibers, and future studies using this approach in small fibers would provide new insights into the peripheral mechanism of neuropathic pain.

1. Introduction

Pain and paresthesias are common manifestations of peripheral nerve injury and one of the major factors that disturb activities of daily living in patients with neuropathy. Neuropathic pain arises from both peripheral and central mechanisms (Campbell and Meyer, 2006), whereas previous experimental studies have shown that changes in the expression, types, and distribution of Na^+ channel in peripheral small sensory axons or neurons following nerve injury could be important for ectopic impulse generation, and thereby neuropathic pain (Cummins and Waxman, 1997; Cummins et al., 2007; Devor et al., 1993; Matzner and Devor, 1994). For motor axons, it has been shown that abnormal muscle cramping is associated with increased nodal Na^+ currents in human axonal neuropathy and motor neuron diseases (Tamura et al., 2006), but the relationship between Na^+ currents in sensory axons and sensory symptoms (neuropathic pain/paresthesias) has rarely been studied in neuropathic patients.

Mexiletine is structurally related to lidocaine and can offer the benefits of Na^+ channel blockade in oral form with high bioavailability instead of repeated intravenous infusion (Dejgard et al., 1988; Jarvis and Coukell, 1998; Oskarsson et al., 1997; Markman and Dworkin, 2006; Stracke et al., 1992). This agent has been tested in several neuropathic conditions and the results were controversial, but previous studies have used only subjective pain rating scale, such as visual analogue scale (Chabal et al., 1992; Jarvis and Coukell, 1998). It would be necessary to assess neuropathic pain more objectively for evaluation of therapeutic effects.

In addition to the classical transient Na^+ channels, there are many different types of Na^+ channels in mammalian axons. Approximately 1.0–2.5% of the total Na^+ channels in human axons are slowly inactivating and active at the resting membrane potential, termed as "persistent" Na^+ channels, and this conductance is

* Corresponding author. Tel.: +81 43 222 7171x5414; fax: +81 43 226 2160.
E-mail address: kuwabara-s@faculty.chiba-u.jp (S. Kuwabara).

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one of the major determinants of axonal excitability (Bostock and Rothwell, 1997). Latent addition using the computerized threshold tracking technique is currently considered the best, non-invasive way to estimate nodal persistent Na^+ conductance *in vivo* (Bostock and Rothwell, 1997). We have used this technique to investigate changes in axonal persistent Na^+ currents in large sensory fibers of patients with neuropathic pain and the effects of mexiletine on pain/paresthesias and axonal excitability. We assessed large myelinated sensory fibers, and therefore the finding cannot be applied to the pathophysiology of small myelinated or unmyelinated fibers which mediate neuropathic pain. However, this approach could be a first step to elucidate ionic mechanisms for neuropathic pain in future studies.

2. Methods

2.1. Subjects

This study enrolled 17 consecutive patients (13 men and 4 women) with painful neuropathy who were referred to the EMG clinic, Chiba University Hospitals, for evaluation of their neuropathy (Table 1). Patients' age ranged from 32 to 75 years (mean, 54 years), and the mean duration from the onset of pain was 19 months (range, 3–84 months). Of the 17 patients, 15 patients had neuropathy caused by diabetes, vasculitis, beriberi, or chemotherapeutic drugs. The remaining two had moderate axonal polyneuropathy, but the cause of neuropathy was not identified, and classified into "idiopathic". All the patients had symmetric sensory-dominant polyneuropathy, and pain/paresthesias in their distal four limbs with mild-to-moderate decreases in touch, pin-prick, and vibratory sensations. In diabetic patients, the hemoglobin A1c (HbA1c) levels ranged from 5.2% to 8.5% (mean, 6.7%). We excluded patients with renal failure, because serum K^+ levels can significantly alter the membrane potential and axonal excitability properties (Kuwabara et al., 2007).

The normal control data of axonal excitability testing were obtained from 35 age-matched healthy subjects (14 men and 21 women; age, 20–86 years; mean 48 years). All patients and normal subjects gave informed consent to the experimental procedures, which was approved by the Ethics Committee of the Chiba University Graduate School of Medicine.

After the clinical and electrophysiologic evaluations, patients received oral mexiletine hydrochloride. The initial dose was 150 mg daily for 1–2 months, gradually increasing up to 450 mg daily if the pain was not relieved (150–450 mg; mean 320 mg). Follow-up assessments were made 3 months after the start of maintenance dose.

2.2. Assessment of neuropathic pain

Patients were asked about the presence of limb pain (burning, lancinating, and pricking pain) and paresthesias (tingling and buzzing). A modified neuropathic pain scale (Dyck et al., 1976) was used to evaluate the extent of disability in performing daily activities: 0, no pain; 1, a complaint but no disability; 2, pain sometimes disturbing work or sleep; 3, severe pain disturbing work or sleep daily. Visual analogue scale (VAS) was also used to estimate the extent of pain/paresthesia. All the 17 patients included in this study had the score 2 or 3. Pain and paresthesias coexisted in all, and therefore severe paresthesia disturbing work or sleep was regarded as pain.

2.3. Latent addition and strength-duration time constant using threshold tracking

The technique of latent addition was performed in the superficial radial sensory axons and median motor axons, using a computerized program (QTRAC with multiple excitability protocol, LA99SDS; ©, Prof. Bostock H, Institute of Neurology, London, UK). For sensory nerve studies, the superficial radial nerve was selected, because sensory nerve action potentials (SNAP) was frequently not recordable or substantially reduced in the median nerve of neuropathy patients. Radial SNAPs were recorded from the anatomical snuff box after stimulation 12 cm proximally at the forearm. The compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis after median nerve stimulation at the wrist (3 cm proximal to the wrist crease). The threshold current required to produce the target response, set to 40% of the maximal SNAP or CMAP amplitude, was determined using a test stimulus of 0.06 ms duration. The test stimulus was conditioned by a hyperpolarizing stimulus from 0.02 to 0.5 ms inter-stimulus test interval, fixed at −90% of the threshold current. The decay of the

Table 1
Clinical and electrodiagnostic profiles of patients with treated with mexiletine.

Patient	Age/sex	Diagnosis	Duration[a] (month)	Nature of pain/paresthesia	Pain disability scale		Reduction of VAS (%)
					Before treatment	After treatment	
1	47/M	Diabetes	12	Pricking	3	1	90
2	47/M	Diabetes	5	Burning/tingling	3	1	88
3	32/M	Diabetes	4	Pricking	3	1	86
4	60/M	Diabetes	4	Tingling	3	1	81
5	48/M	Diabetes	6	Burning/tingling	3	1	80
6	68/M	Diabetes	6	Burning/tingling	3	1	71
7	49/F	Vasculitis	7	Pricking/tingling	3	1	71
8	55/F	Idiopathic	5	Burning	3	1	60
9	72/M	Diabetes	58	Pricking	3	1	60
10	38/M	Diabetes	3	Pricking/burning	3	1	50
11	57/M	Diabetes	5	Pricking	3	1	50
12	73/F	Drug induced	60	Pricking/tingling	3	2	70
13	38/M	Diabetes	2	Pricking/tingling	3	2	50
14	45/M	Beriberi	40	Pricking	3	2	50
15	58/M	Idiopathic	12	Pricking	3	2	43
16	75/M	Diabetes	12	Pricking/tingling	3	3	0
17	52/M	Diabetes	84	Pricking/tingling	2	2	20
Median (range)			7 (3–84)		3 (2–3)	1 (1–3)*	60 (0–90)

Data are given according to the pain disability scale and visual analogue scale reduction.
VAS = visual analogue scale.
[a] Duration from the onset of pain.
* $p < 0.001$, compared with scores before treatment.