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Strength-duration properties and glycemic control in human diabetic motor nerves

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Abstract

Objective: To investigate the influences of hyperglycemia on axonal excitability in human diabetic nerves. Hyperglycemia results in decreased Na^+–K^+ pump function, presumably leading to intra-axonal Na^+ accumulation and thereby, reduced Na^+ currents.

Methods: The strength-duration time constant (τ_{SD}), which partly depends on persistent Na^+ conductance active at the resting membrane potential, was measured in median motor axons of 79 diabetic patients. The relationship of τ_{SD} with the state of glycemic control (hemoglobin A1c [HbA1c] levels) was analyzed.

Results: The mean τ_{SD} was longer for diabetic patients than for normal controls, but the difference was not significant. Among diabetic patients, the subgroup of patients with good glycemic control (HbA1c $<7\%$) had significantly longer τ_{SD} than the patient group with poor control (HbA1c $>9\%$; $P=0.04$). The mean τ_{SD} was longest at the HbA1c level of 5–6%, gradually decreasing and reaching a plateau around the HbA1c level of 9%. There was an inverse relationship between HbA1c levels and τ_{SD}, when the HbA1c levels ranged from 5 to 9% ($P=0.04$).

Conclusions: In diabetic nerves, τ_{SD} is generally longer than normal, but hyperglycemia is associated with paradoxically shortened τ_{SD}, because of a decrease in axonal persistent Na^+ conductance, possibly related to reduced membranous Na^+ gradient, tissue acidosis, or other metabolic factors.

Significance: Measurements of τ_{SD} could provide a new insight into changes in ionic conductance in human diabetic nerves.

Keywords: Strength-duration time constant; Diabetes mellitus; Diabetic neuropathy; Glycemic control; Sodium gradient

1. Introduction

The pathophysiology of diabetic neuropathy includes a complex interplay between metabolic abnormalities directly related with hyperglycemia and structural nerve damage caused by microangiopathy (Sima, 1996; Dyck and Giannini, 1996). There are several lines of evidence that metabolic factors such as activation of polyol pathway and a decrease in Na^+-K^+ ATPase activity play an important role in the development of diabetic neuropathy (Greene et al., 1987; Sima, 1996). The conversion of excess glucose to sorbitol, and the resulting depletion of myo-inositol that leads to reduced Na^+–K^+ ATPase activity, are major metabolic factors responsible for nerve dysfunction. Experimental studies using the voltage clamp analysis showed decreases in the Na^+ gradient across the axolemma resulting in reduced Na^+ currents in diabetic rats. (Brismar et al., 1987, 1993).

In addition to the classical transient Na^+ channels, there are many different types of Na^+ channels in mammalian axons. In human motor axons, approximately 1% of the total Na^+ channels are active at the resting membrane potential, termed as 'persistent' Na^+ channels (Bostock and Rothwell, 1997). Insight into persistent Na^+ conductance in human axons can come from studies of strength-duration properties (Mogyoros et al., 1996, 1998; Bostock et al., 1998). The strength-duration time constant (τ_{SD}) is a classical measure of axonal excitability, and is partly dependent on persistent

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Na^+ conductance (Baker and Bostock, 1997; Bostock and Rothwell, 1997; Mogyoros et al., 1998). If the trans-axonal Na^+ gradient is reduced in diabetic nerves, their persistent Na^+ conductance would decrease. To investigate this hypothesis, we measured τ_{SD} in a large number of diabetic patients, and studied the relationship of τ_{SD} with the state of glycemic control.

2. Methods

2.1. Patients

A total of 79 patients with diabetes mellitus, referred to the EMG clinic, Chiba University Hospital between October 2000 and April 2004, were studied. Ten had type 1 diabetes mellitus, and the remaining 69 had type 2 diabetes. They ranged in age from 19 to 82 years (mean, 57 years) with a disease duration of 1–32 years (mean, 11 years). Sixty-seven of the patients had mild-to-moderate symptomatic neuropathy, and the remaining 12 were asymptomatic with normal nerve conduction studies. We excluded patients with symptomatic carpal tunnel syndrome and a severely decreased compound muscle action potential (CMAP; <2 mV) in median nerve conduction studies. We also excluded patients with renal failure because serum K^+ levels can significantly alter the membrane potential and excitability indices (Kiernan et al., 2002). Of the 79 patients, 34 had received insulin treatment, 28 were treated with oral antidiabetic medication, and 17 were on diet only.

The normal control data of strength-duration properties were obtained from 26 age-matched healthy subjects (16 male and 10 female; age, 40–84 years; mean age, 57 years). Sixteen patients with non-diabetic axonal neuropathy served as neurological controls; neuropathies included vitamin B1 deficiency, vasculitic neuropathy, and acute motor axonal neuropathy. All patients and normal subjects gave informed consent to the experimental procedures, which were approved by the Ethics Committee of the Chiba University School of Medicine.

2.2. Measurements of strength-duration properties

Strength-duration properties (τ_{SD}, rheobase, and stimulus-response curves) were measured using 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 and Bostock, 2000; Kiernan et al., 2000, 2002; Kuwabara et al., 2000, 2002; Kanai et al., 2003). The median CMAP was recorded from the abductor pollicis brevis after stimulation at the wrist (3 cm proximal to the wrist crease). Skin temperature was measured near the stimulating site, and maintained above 32.0 °C using a heater, if necessary. The protocol began with the measurement of stimulus response curves using test stimuli 0.2 and 1.0 ms in duration. From these curves, the strength-duration time constant (τ_{SD}) and rheobasic current (I_{rh}), were calculated using the formula (Kiernan et al., 2000; Kanai et al., 2003)

$$\tau_{SD} = 0.2(I_{0.2} - I_{1.0})/(I_{1.0} - 0.2I_{0.2})$$

$$I_{rh} = 1.25(I_{1.0} - 0.2I_{0.2})$$

where $I_{0.2}$ and $I_{1.0}$ are the respective threshold currents for test stimuli of 0.2 and 1.0 ms duration. The currents required to produce CMAPs of 10–90% of the maximal CMAP were measured from the stimulus response curves, and used to calculate the τ_{SD} for CMAPs of different sizes. τ_{SD} is defined as the ratio between the minimum charge threshold and the I_{rh}, and is equal to the chronaxie. I_{rh} is defined as the threshold current for a stimulus of infinitely long duration (Bostock et al., 1998; Burke et al., 2001).

2.3. Statistical analysis

For statistical analysis, differences in the median values among groups were compared by analysis of variance with post hoc analysis (Fisher's protected least significant difference). Regression analyses were made using the Spearman rank correlation test.

3. Results

3.1. Strength-duration time constant (τ_{SD})

Fig. 1A shows the mean τ_{SD} in normal controls, diabetic patients, and patients with non-diabetic neuropathy. τ_{SD} was longer in diabetic patients than in normal subjects, but the difference was not statistically significant: the mean $\pm$SEM value was 0.40 ± 0.01 ms for normal controls, 0.43 ± 0.01 ms for diabetic patients and 0.46 ± 0.02 ms for neuropathy controls. τ_{SD} was significantly longer for patients with non-diabetic neuropathy than for normal controls ($P = 0.03$).

Fig. 1B shows τ_{SD} of subgroups of diabetic patients. Patients were divided into the three subgroups according to the HbA1c levels: (1) good, HbA1c $<7.0\%$; (2) fair, 7.0–9.0%; (3) poor, $>9.0\%$. The mean τ_{SD} was significantly longer in patients with good glycemic control than in normal subjects ($P = 0.02$) and in patients with poor control ($P = 0.04$). Table 1 shows clinical profiles and results of median nerve conduction studies in each patient group. All nerve conduction parameters in the three patient groups were significantly different from the normal values, but similar among the patient groups, suggesting that the extent of nerve structural changes was not significantly different among the patient groups. Tibial motor nerve studies and sural sensory nerve studies showed similar results.

To further investigate the effects of hyperglycemia on τ_{SD}, patients were divided into subgroups according to