Motor unit number estimate as a predictor of motor dysfunction in an animal model of type 1 diabetes

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Souayah N, Potian JG, Garcia CC, Krivitskaya N, Boone C, Routh VH, McArdle JJ. Motor unit number estimate as a predictor of motor dysfunction in an animal model of type 1 diabetes. Am J Physiol Endocrinol Metab 297: E602–E608, 2009.First published July 14, 2009; doi:10.1152/ajpendo.00245.2009.—Peripheral neuropathy is a common complication of diabetes that leads to severe morbidity. In this study, we investigated the sensitivity of motor unit number estimate (MUNE) to detect early motor axon dysfunction in streptozotocin (STZ)-treated mice. We compared the findings with in vitro changes in the morphology and electrophysiology of the neuromuscular junction. Adult Thy1-YFP and Swiss Webster mice were made diabetic following three interdaily intraperitoneal STZ injections. Splay testing and rotarod performance assessed motor activity for 6 wk. Electromyography was carried out in the same time course, and compound muscle action potential (CMAP) amplitude, latency, and MUNE were estimated. Two-electrode voltage clamp was used to calculate quantal content (QC) of evoked transmitter release. We found that an early reduction in MUNE was evident before a detectable decline of motor activity. CMAP amplitude was not altered. MUNE decrease accompanied a drop of end-plate current amplitude and QC. We also observed small axonal loss, sprouting of nerve endings, and fragmentation of acetylcholine receptor clusters at the motor end plate. Our results suggest an early remodeling of motor units through the course of diabetic neuropathy, which can be readily detected by the MUNE technique. The early detection of MUNE anomalies is significant because it suggests that molecular changes associated with pathology and leading to neurodegeneration might already be occurring at this stage. Therefore, trials of interventions to prevent motor axon dysfunction in diabetic neuropathy should be administered at early stages of the disorder.

Motor unit number estimate (MUNE) is derived from the work of McComas et al. (29) and provides a unique electrophysiological tool to estimate the number of axons innervating a muscle. MUNE is computed from the ratio between maximum muscle CMAP divided by the average surface motor unit potential. Although MUNE technique is increasingly used in clinical and experimental studies of amyotrophic lateral sclerosis (ALS), it is rarely used in other peripheral nerve disorders, including diabetic neuropathy (6, 18, 26, 34).

In contrast to the limitation of CMAP amplitude noted above, MUNE reflection of motor unit loss is not affected by compensatory muscle reinnervation, especially at early stages of motor unit remodeling (7, 31). Thus, MUNE may offer the advantage of early quantitative detection of motor unit abnormalities during a silent period of diabetic neuropathy where both the clinical and traditional electrodiagnostic parameters are normal (10, 29, 39, 42). To test this hypothesis, we investigated whether MUNE is a more sensitive indicator of motor axon dysfunction than CMAP amplitude analysis in an animal model of type 1 diabetes. Because a decline of MUNE could be limited to a distal axonopathy without loss of motor axons or to a functional remodeling of the neuromuscular junction or motor units (42, 46), we also investigated in vitro changes in the morphology and electrophysiology of the neuromuscular junction in type 1 diabetic mice.

MATERIALS AND METHODS

Animals and tissue preparation. Adult Thy1-YFP (YFP transgenic) and Swiss Webster mice were housed and cared for in our Institutional Animal Care Facility. Experimental protocols were approved by the Institutional Animal Care and Use Committee of the New Jersey Medical School. Five- to six-week old mice were made diabetic with intraperitoneal (ip) injections of streptozotocin (STZ; Sigma-Aldrich, St. Louis, MO) according to the following schedule: day 1, 100 mg/kg; day 3, 60 mg/kg; day 5, 60 mg/kg. Control mice used for electrophysiological recordings received similar ip injections of the citrate buffer vehicle. Blood glucose levels were monitored biweekly with a commercial glucometer (One Touch Ultra). Levels >450 mg/dl signaled hyperglycemia.

Rotarod analysis. Mice were trained to walk on a horizontal rod rotating at 4 rpm (Rotamex; Columbus Instruments, Columbus, OH). This initial phase of training lasted 3 days and involved three trials of 5 min/trial. On day 4, the rotation rate was progressively increased by 4 rpm every 40 s until a maximum velocity of 40 rpm was reached or the mouse fell from the rod. The time of walk on the rod was measured with the later protocol at 0 (control), 2, 4, and 6 wk after hyperglycemia had been established. To obtain a muscle performance score, mice were subjected to two trials/wk three times/day. The time to fall from the rotating rod was averaged for each time point.

Behavioral motor function. Behavioral motor function was assessed by the splay test. Animals were held by the end of the tail and...
evaluated for the ability to spread their hindlimbs. Mice with hindlimb dysfunction were scored from 0 (control) to 3 (most severe dysfunction) as follows. If the mouse extended its legs straight out when lifted by the tail, the score was 0. If the mouse extended its legs but not far from the body, the score was 1. If the mouse could only minimally extend its legs it received a score of 2, and if the mouse could not move its hindlimbs the score was 3.

In vivo electrodiagnostic studies. Mice were anesthetized with a rodent cocktail of ketamine (80 mg/kg)/xylazine (10 mg/kg) injected ip. The abdomen and distal hindlimbs were shaved, and animals were taped prone to a polystyrene foam board. Skin temperature was maintained by heated pad and kept above 32°C. The stimulating electrodes were 0.7-mm needles insulated with Teflon (Dantec sensory needle; Dantec, Skovlunde, Denmark). The cathode was placed close to the sciatic nerve at the proximal thigh, and the anode was placed subcutaneously 1 cm proximal to the anode. Motor responses were recorded from a ring electrode (Hush micro digital rings; Alpine Biomed, Fountain Valley, CA) that was placed circumferentially around the animal’s hindlimb at 1–1.5 cm distance from the stimulating electrode. Activity was recorded in both flexor and extensor compartments. The reference ring electrode was placed circumferentially around the hindlimb, 2 cm distal to the recording electrode. Recordings were performed on both hindlimbs. Stimuli were given with monophasic pulses from a Medtronic Keypoint (Medtronic, Minneapolis, MN) through a constant current stimulator and delivered with a fine intensity control. Recordings were made with Medtronic Keypoint electromyography amplifiers (Medtronic). Data were collected on a computer and stored digitally for online (real-time) analysis. Filter settings were 500 Hz/5 KHz. For all studies, the position of the stimulating electrode was optimized by establishing a threshold for evoking a motor response at <0.7 mA. Stimulus intensity was increased until the CMAP was maximized. Potential amplitude (peak-peak) and distal incremental MUNE was performed at a standard amplifier gain using a modification of the technique described previously by McComas et al. (29) and used by Shefner (39) in mice. Using a repetition rate of 1/s, the stimulus intensity was slowly increased from subthreshold levels until a small all-or-none response was evoked. The response was digitally recorded after its stability was established by three to four identical repeats. The intensity was slowly augmented until the response increased in a quantal fashion. The increased response was again monitored for stability before a tracing was obtained for analysis. This process was repeated for a total of 10 increments. Before 10 increments were performed, a supramaximal response was obtained and used to calculate maximum CMAP area. Individual motor unit area was determined by subtracting the CMAP area of each response from that of the prior response. The average of individual values yielded an estimate of average single motor unit action potential area. The area of the maximum CMAP was divided by the preceding value to yield the MUNE. Average motor unit size was calculated by dividing maximum CMAP area by the corresponding MUNE value.

In vitro electrophysiology. At 4 and 7 wk after onset of hyperglycemia, mice were anesthetized with isoflurane and euthanized by cervical dislocation, and extensor digitorum longus (EDL) and/or Triangularis sterni nerve muscle preparations were dissected for study. Dissected nerve muscle preparations were pinned to a Sylgard-lined Plexiglas chamber and bathed in HEPES-Ringer’s solution (HRS) containing 135 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 5.5 mM dextrose, and 5 mM HEPES (Sigma-Aldrich); 0.75 μM α-conotoxin GIIIB (Bachem, Torrance, CA) was added to the bath to inhibit muscle action potentials and mechanical responses to nerve stimulation. Electrical activity of the motor end plate was recorded with two-electrode voltage clamp. The electrodes were inserted into the end plate membrane at an interelectrode distance of ~50 μm. One electrode filled with potassium acetate (4 M) delivered current. The other electrode filled with potassium chloride (3 M) recorded membrane voltage. End plate currents (EPCs) were elicited by stimulating the nerve at 1 Hz. EPC and miniature end plate currents (mEPCs) were amplified (Axoclamp-2B; Axon Instruments, Foster City, CA), digitized (Digidata 1200; Axon Instruments), and acquired/analyzed with pClamp software (version 9.2; Axon Instruments). Currents were recorded at a holding potential of ~75 mV.

Imaging of motor nerve endings and muscle end plates. To visualize motor end plates, Triangularis sterni nerve muscle preparations excised from YFP mice were bathed for 15 min in HRS containing 1 μM α-bungarotoxin (BuTX) (Alexa 647 α-BuTX; Sigma-Aldrich). After a final wash in toxin-free HRS for 20 min, motor nerve endings and muscle end plates were visualized using an upright fluorescence microscope (Olympus BX61WI). Metamorph Software (Molecular Devices, Downingtown, PA) was used to acquire images of the mouse nerve endings and muscle end plates.

Data presentation and statistical analyses. Data were analyzed and plotted with pClamp, Sigmaplot (SPSS, Chicago, IL), and GraphPad Prism (GraphPad Software, San Diego, CA) programs. Data are presented as means ± SE. One-way ANOVA with Tukey post hoc test compared experimental and control mean values; P < 0.05 indicated a significant difference.

RESULTS

Type 1 diabetes decreases MUNE. Seven days after the last STZ injection, all mice had glucose levels >450 mg/dl (maximum by commercial glucometer). Glycemia levels remained elevated throughout the course of the study (Table 1). Mouse body weight at the beginning of the study was 27.84 ± 3.43 g. At 6 wk after the onset of hyperglycemia, body weight had increased to 37.74 ± 1.08 and 41.03 ± 2.63 g for diabetic and control mice, respectively. Bilateral measurement of MUNE, CMAP amplitude, and distal latency of motor nerve conduction were made for 28 adult (20–25 g) Thy1-YFP (YFP) mice before as well as at 2, 4, and 6 wk after STZ treatment. Control MUNE was 280.15 ± 8.55. Following STZ treatment, MUNE significantly (P < 0.0001) decreased to 197.54 ± 10.41 at 2 wk and 134.12 ± 9.83 at 6 wk after onset of hyperglycemia (Fig. 1). In contrast, CMAP and distal latency remained equivalent to control throughout the 6-wk time course of this study (Fig. 2). That is, the control values of CMAP amplitude and distal latency of 12.9 ± 0.8 mV and 1.2 ± 0.04 ms, respectively, were statistically equivalent to 12.2 ± 1.6 mV and 1.47 ± 0.8 ms at the 6-wk time point.

Average motor unit size increased following STZ-induced diabetes. That is, average motor unit size was 51.53 ± 4.92 mVms before and 64.43 ± 5.47 mVms at 2 wk after diabetes onset. The magnitude of this increase became statistically significant (P < 0.0001) at 4 and 6 wk when the average motor unit size was 89.73 ± 6.76 and 98.07 ± 13.76 mVms, respectively (Fig. 3). The correlation coefficient was −0.9167 for the relation between MUNE reduction and motor unit size increase.

Table 1. Blood glucose concentration at various times after mice were treated with STZ

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<th>Week</th>
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<td>2</td>
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STZ, streptozotocin. Glycemia levels remained above 450 mg/dl throughout the course of the study. Glycose levels were routinely monitored at all stages of the experimental process; 450 mg/dl represents the maximum range value of the commercial glucometer.
### Motor function assessment.

Splay testing suggested relative preservation of motor function until the 4th week after induction of diabetes. That is, the average splay scores were 0, 1, 2, and 3 for weeks 0, 2, 4, and 6, respectively. Rotarod testing suggested a progressive, but not statistically significant, decline in motor performance after 6 wk of hyperglycemia. That is, the times on the rotarod were 321.7 ± 31.78, 352 ± 42.96, 289.6 ± 41.85, and 260.5 ± 41.74 s at 0 (control), 2, 4, and 6 wk, respectively, after onset of hyperglycemia (Fig. 4).

Chronic hyperglycemia is associated with progressive changes in the function and morphology of the neuromuscular junction. In vitro electrophysiology was performed on neuromuscular junctions of the fast-twitch EDL muscle of Swiss Webster mice. mEPC amplitude increased significantly ($P < 0.0001$) to 2.1 ± 0.01 nA (9 = 3,930 events from 18 neuromuscular junctions (NMJ) of 4 mice) from the control value of 1.87 ± 0.01 nA (9 = 4,840 events from 20 NMJ of 4 mice) at 4 wk after the onset of STZ-induced hyperglycemia. Subsequently, mEPC amplitude significantly ($P < 0.05$) decreased to 1.84 ± 0.01 nA (9 = 3,708 events from 19 NMJ of 4 mice) at 7 wk after the onset of hyperglycemia (Fig. 5). In contrast to spontaneous mEPC, stimulus-evoked EPC amplitude declined continuously over the time course of hyperglycemia (Fig. 6). That is, mean EPC amplitude decreased from the control value of 146.4 ± 18.54 (9 = 299 events from 20 NMJ of 4 mice) to 95.1 ± 15.60 (9 = 101 events from 18 NMJ of 4 mice) and 53.7 ± 9.43 nA (9 = 237 events from 19 NMJ of 4 mice) at 4 and 7 wk, respectively, after the onset of hyperglycemia. The decline of EPC amplitude during hyperglycemia was due to a reduction of the mean number of quanta released in response to nerve stimulation (1 Hz). That is, mean quantal content (QC) declined from the control value of 60.05 ± 11.35 to 42.4 ± 4.9 and 36.9 ± 4.6 at 4 and 7 wk, respectively, after the onset of hyperglycemia (Fig. 7).

The preceding functional changes occurred in parallel with changes in the clustering of acetylcholine (ACh) receptors (AChRs) on the motor end plate. Figure 8, A and B, presents typical rhodamine α-BuTX-labeled motor end plates in the *Triangularis sterni* muscle of a normal YFP mouse. Note that the green labeled motor nerve ending fills the toxin-labeled end plate. Figure 8C presents a neuromuscular junction of a mouse at 4 wk after the onset of STZ-induced hyperglycemia. In this preparation, the pattern of AChR distribution is more delicate and fragmented with small "islands" of receptors that seem to have dissociated from the main receptor cluster. The circled arrows in this image point to nerves that appear to have sprouted from within the nerve terminal to innervate isolated end plate areas of AChR clusters (Fig. 8). At this time point, motor end plate size, measured as the perimeter of the BuTX-stained membrane surface, was not significantly different [323 ± 22.17 arbitrary units (AU); 9 = 18 end plates in 3
mice] compared with control (372.2 ± 26.91 AU; n = 13 end plates in 3 mice).

DISCUSSION

Peripheral neuropathy is a common complication of type 1 diabetes. Affected patients may exhibit severe limb pain or loss of sensation in a “stocking and glove” distribution at an early stage of the neuropathy without substantial motor axon loss (37). Later in the course of the diabetes, motor dysfunction may occur, leading to distal muscle weakness and atrophy (1, 37, 43). Similar to what is observed in human studies, animal models of type 1 diabetes display greater vulnerability of the sensory peripheral nerve compared with the peripheral motor nerve (13, 23, 27, 45, 50). In contrast, our work demonstrates that there is a significant reduction in MUNE at 2 wk after hyperglycemia onset with a concomitant increase of mean motor unit size. We also observed that CMAP amplitude and motor strength were relatively spared. These findings imply that remodeling of motor units occurs early in the course of diabetic neuropathy. MUNE can detect motor unit abnormalities even in the absence of noticeable clinical deficits or significant motor neuron loss in diabetic neuropathy mice. The early detection of MUNE anomalies is significant because it suggests that molecular changes associated with pathology and leading to delayed neurodegeneration might already be occurring at this stage. Therefore, trials of interventions to prevent motor axon loss in diabetic neuropathy should probably be

Fig. 4. Type 1 diabetic mice have decreased motor function. Mice performed for shorter intervals on the rotarod treadmill after onset of diabetes over the 6-wk period; however, the decline was not statistically significant from prediabetic states. Mice also exhibited reduced mobility along with severe weight loss. Bars represent average times ± SE obtained from 6 mice.

Fig. 5. Miniature end plate current (mEPC) amplitude of the extensor digitorum longus (EDL) muscle significantly (**) P < 0.0001) increases relative to control (0-wk time point) at 4 wk after the onset of STZ-induced hyperglycemia. At 7 wk, mEPC amplitude was significantly less than control (**P < 0.05). Bars represent means ± SE obtained from 4 to 5 cells for each of 4 muscles (40–200 mEPCs/cell).

Fig. 6. EPC amplitude of the EDL muscle is significantly (*) P < 0.05) less than control (0-wk time point) at 4 and 7 wk after onset of STZ-induced hyperglycemia. Bars represent averages ± SE obtained from 4 to 5 cells for each of 4 muscles (10–15 EPCs/cell).

Fig. 7. Mean quantal content is significantly (*) P < 0.05) less than control (0-wk time point) at 7 wk after the onset of STZ-induced hyperglycemia. Bars represent the mean ± SE for quantal content of 4 separate EDL muscles at each time point. These means were calculated for the ratio of average EPC amplitude to average mEPC amplitude obtained for 9–16 end plates from each muscle.
administered at an early stage of the disorder prior to neuronal degeneration.

Abnormalities in MUNE before detectable alterations in behavior or motor axon density have also been reported in the mutant superoxide dismutase mouse, an animal model of ALS, and in plasma membrane Ca\(^{2+}\)-ATPase (PMCA)2-heterozygous mice at 2–3 mo of age (42, 46). The early MUNE alteration observed in our study may reflect an exclusive physiological, rather than a structural, alteration of the axon. The limited sprouting of intact axons (Fig. 8) supports this hypothesis. Furthermore, Ramji et al. (35) reported a reduction of nerve conduction velocity in the STZ model of type 1 diabetes in the absence of axonal atrophy or myelin loss. However, Ramji et al. (35) did not find changes in CMAP amplitude until 4 mo after hyperglycemia was established. At the same time, these authors failed to detect early changes in MUNE in their STZ treated CD-1 mice. This contrasting finding might be explained by the different dosing of STZ treatment. With our treatment protocol, mice develop constant elevated (25 mmol/l) hyperglycemia after the first week of STZ injections. In contrast, Ramji et al. (35) reported glycemia levels greater than 16 mmol/l after 1 mo of treatment. Therefore, it is possible that MUNE did not decline during the first month of their study because mice were not severely hyperglycemic.

Early metabolic axonal alterations, such as impaired Na\(^{+}\)/K\(^{+}\) ATPase activity, may contribute to early motor unit functional remodeling (44). In our studies, we used the incremental MUNE method, which assumes that each response increment resulting from graded stimulation represents the addition of a single motor unit. However, because the threshold for a given motor unit is probabilistic rather than absolute, a constant repetitive stimulus may evoke responses from different motor units at different times (8, 32, 33, 40). Another assumption of MUNE analysis is that the motor units measured at low stimulus intensity and used in the calculation of the average motor unit size are representative of the total population of motor units in the entire muscle (40). Alternatively, the incremental MUNE technique may omit small surface motor unit potentials (S-MUPS) to improve reproducibility (S-MUP negative peak amplitude <10 \(\mu\)V) (22, 48, 49). In a chronic denervating process, such as diabetic neuropathy, sprouting of intact small motor units may result in larger S-MUPS that rise above the threshold of MUNE technique detection. This may inflate the estimated number of motor units by adding these new and larger S-MUPS, which are omitted in healthy conditions. As a result, the loss of small S-MUPS may be underestimated, limiting the sensitivity of MUNE to early small motor unit changes in diabetic neuropathy (49). Although MUNE was significantly reduced as early as 2 wk after hyperglycemia, this reduction could be more prominent if small S-MUPS were included. Finally, motor axon instability in response to repeated electrical stimulation may add another source of error to the estimation of the number of motor units in pathological conditions (22).

Despite these technical limitations, the incremental MUNE method has been used successfully in several neuromuscular disorders and has provided insights into pathogenesis (3–5, 11, 12, 15, 18, 20, 30, 39–42). In particular, MUNE has been applied in human diabetic neuropathy. Hansen and Ballantyne (18, 19) found MUNE to be reduced in both uremic and diabetic neuropathies, with diabetic patients showing more evidence of compensatory reinnervation on the basis of individual motor unit size. These electrodiagnostic findings are supported by pathological studies suggesting more reinnervation in diabetic than uremic nerves (39). MUNE has also detected motor neuron loss in animal models of ALS. This includes the ALS2/alsin mouse model carrying a disrupted gene responsible for a number of juvenile recessive motor neuron diseases in humans (2, 15, 17, 39, 40).
A motor unit comprises a single motor neuron and the group of muscle fibers it innervates. The increase in mean motor unit size suggests either a preferential loss of smaller motor units or enlargement of these units through compensatory sprouting (35). If motor units are lost, force production will decrease in parallel, accounting for the muscle weakness described in diabetic patients. Motor unit size may also increase by axonal sprouting, which reinnervates denervated muscle fibers to compensate for loss of adjacent functional motor units (16, 35, 47). Although some sprouting was identified in our imaging of motor nerve endings, it was not sufficient to explain the dramatic alteration of single motor unit size in our animal model of diabetes. It is possible that downregulation of molecular nerve protective factors such as IGF-I may cause the lack of significant compensatory sprouting in our animal model of diabetes (21, 35). In our work, fluorescent images of nerve terminals and neuromuscular junctions of the Triangularis sterni muscles of Thy1-YFP mice equilibrated with Alexa 647 α-BuTX demonstrated end plate fragmentation (Fig. 8C), resulting in the formation of patches or islands of receptors. Similar results have been reported by Ramji et al. (35) and Marques and Santo Neto (28). These findings are consistent with distal retraction of the axon terminal. Axonal distal retraction without loss of motor axons was proposed to explain the alteration in single motor unit size without reduction in the number of motor units in an animal model of motor neuron disease and in PMCA2-heterozygous mice (42, 46). The observed increase in single motor unit size could be explained by the end plate fragmentation noticed in our study (in the absence of prominent axonal sprouting) if small motor units were especially involved (35).

Additionally, we demonstrated a significant increase of mEPC amplitude after 4 wk of hyperglycemia that could be explained by altered ACCh metabolism. In the end plate area, the enzyme acetylcholinesterase (AChE) is responsible for ACCh hydrolysis. Changes on ACCh activity occur in experimental type 1 diabetes (25), which contrasts with increased activity of the enzyme in cerebral cortex and serum (38). Retinal ACCh appears to be intact during diabetes (38). The activity of ACCh at the NMJ of diabetics has not been fully investigated. However, the oligomerization pattern of ACCh is altered in diabetic rat skeletal muscle (25). Therefore, we do not rule out a decrease in ACCh activity at the NMJ to account for the increase of mEPC amplitude.

Interestingly, at 7 wk of hyperglycemia, mEPC amplitude decreases. The reduced amplitude of synaptic current could be explained partly by a decrease in AChR density at the end plate area. In fact, Ramji et al. (35) reported a loss of ACChr in the STZ model of diabetes. However, the change was noticed only after long-term (8 mo) chronic hyperglycemia compared with the earlier occurrence in our study.

We also found a large decline of EPC amplitudes. In parallel, the mean QC of EPCs was significantly reduced in the EDL after 7 wk of hyperglycemia. Constantini et al. (9) also reported a decrease of QC at the NMJ of rats after 3.5 mo of experimental diabetes. A reduction in QC suggests alteration of motor nerve terminal function during early stages of diabetic neuropathy. Such subtle alterations might influence functional neuromuscular transmission (36).

A number of experimental reports support our findings and suggest early pathological changes in diabetic NMJs. Fahim et al. (14) examined the dorsiflexor muscle from STZ-diabetic mice. At 2 wk after STZ was administered, they observed reductions in the amplitude of both resting membrane potential and miniature end plate potentials. These authors also describe fewer synaptic vesicles and mitochondrial abnormalities as well as ultrastructural changes in the diabetic NMJ similar to those of motor neuron disorder and aging (13, 14). These later observations could help explain the reduction in QC seen in our diabetic mice. In accord with our study, Kimura et al. (24) found a reduction in stimulus-evoked transmitter release from motor nerve endings of diabetic mice. Furthermore, the sternomastoid muscle of nonobese diabetic mice exhibits an altered distribution of muscle end plate ACChRs with the formation of abnormal receptor islands and motor nerve terminal sprouts (28) similar to those we report for the STZ model of diabetes. All of these changes precede any gross decline of motor function, as confirmed by the performance of the animal on the rotarod.

In summary, our study demonstrates significant reduction of MUNE at early stages of diabetic neuropathy when clinical, behavioral, and classic in vivo neurophysiological studies are unaltered and when morphological changes are subtle. The alterations in transmission across the NMJ with minor axonal loss or sprouting that parallel MUNE decline suggest that functional remodeling of motor units occurs early in the course of diabetic neuropathy. This finding challenges the belief that motor neurons are resistant to diabetic damage. An understanding of the molecular mechanisms leading to motor nerve pathological changes that might be occurring at an early stage of diabetes may offer a window for a trial of interventions to prevent peripheral neural loss during diabetic neuropathy.

REFERENCES

MOTOR UNIT NUMBER ESTIMATE IN TYPE 1 DIABETES


