Original Article

Effect of hyperglycemia on conduction parameters of tibial nerve's fibers to different muscles: A rat model

Çağdaş Erdoğan, Utku Cenikli, Eylem Değirmenci, Attila Oğuzhanoğlu

Department of Neurology, Pamukkale University, Denizli, Turkey

ABSTRACT

Introduction: Routine conduction studies reflect the summation of all nerve fibers in a peripheral nerve. Nerve fiber groups to distal, small muscles have smaller diameters than the ones to large proximal muscles. There may be minimal differences between the diameters of nerve fiber groups innervating different muscles; even they are all same type of fibers. So, in neuropathic processes some nerve fiber groups may be more seriously affected. **Materials and Methods:** 14 rats (7 diabetic, 7 control) were studied. Tibial nerve was stimulated from two points and while recorded from a distal (foot intrinsic muscles) and a proximal (gastrocnemius) muscle. **Results:** There was a significant difference between the proximal and distal recorded conduction velocities. Both proximal and distal recorded conduction velocities decreased during the hyperglycemic process. **Discussion:** Our method successfully demonstrated different nerve fiber groups; but, the neuropathic process seemed to be homogeneous in both fiber groups.

Key words: Different nerve fiber groups in the same nerve, hyperglycemia, rat

Introduction

Diabetic polyneuropathy (PNP) is one of the main causes of morbidity in patients with diabetes mellitus (DM).[1] More than 80% of the patients with clinical diabetic neuropathy have a distal symmetrical form of this neuropathy that progresses following a fibre-length dependent pattern.[2] Conventional conduction studies which reflect the involvement of large nerve fibers have been used to evaluate diabetic polyneuropathy in clinical practice. However, diabetic patients may experience neuropathic pain even when the conventional electrophysiological studies are normal. This clinical problem caused the development of new diagnostic techniques to evaluate the underlying neuropathic processes in DM.

Recent studies have shown that distal and smaller nerve fibers are more sensitive to hyperglycemia, but methods used to detect small fiber neuropathies are difficult and expensive for the routine examination.[3] The electrophysiological methods that investigate the patterns of nerve involvement in DM have been performed by testing different peripheral nerves; however involvement in the same peripheric nerve segment is not clear.[4]

It is known that the nerve fibers, which are innervating different muscles, travel separately in the same segment of the peripheric nerve and bigger muscles have bigger motor units.[5-7] The size of the neuron body seems to correlate with the diameter of its nerve fiber groups.[8] Oguzhanoglu *et al*. reported that larger muscles are innervated by larger and faster fibers than the small muscles' fibers.[9] As the conduction velocity of a nerve fiber correlates with its diameter, it may be possible to demonstrate this difference when two different nerves fiber groups of the same nerve are electrophysiologically studied.

Routine conduction studies of a motor nerve allow us to identify the existence of involvement. The nerve is defined as normal if the conduction parameters are within normal limits. This may be accepted if the nerve included same diametered nerve fibers. But as we mentioned above although they all are same type of nerve fibers, there are minimal differences in diameters among different nerve fiber groups even in the same segment of the peripheric nerve. So some nerve fiber groups may be predominantly affected although some are relatively spared.

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Address for correspondence:
Dr. Çaðdaþ Erdoğan, Kinikli, Denizli, Turkey. E-mail: drcagdaserdogan@gmail.com

Conduction parameters of two different nerve fiber groups could be evaluated by stimulating on the same site and recording from two different muscles groups.[9] This method would be helpful to evaluate different involvement types of nerve fiber groups, even in the same peripheric nerve and to understand the patho-physiological processes of neuropathy.

With this purpose, we aimed to demonstrate the conduction parameters of different nerve fiber groups in the same peripheral nerve segment and to figure out the effects of hyperglycemia on these different nerve fiber groups.

Materials and Methods

Animals

14 male, 8 months old, Wistar albino rats were used. Animal care and experimental procedures were approved by the ethics committee in human and animal experimentation of the Pamukkale University Ethical Committee. Rats were divided into two equal groups; diabetic group ($n = 7$) and the control group ($n = 7$). All rats' basal weight and blood glucose levels were recorded with the same glucometer and the blood measurements were repeated on the 3rd and 10th. In addition basal weight and blood glucose levels of the rats' were also recorded before the all electrophysiological studies (ES).

Hyperglycemia was induced by the intraperitoneal (I.P.) administration of 60 mg/kg streptozotocine (STZ) after the first ES day. Same amount of saline was injected to control group intraperitoneally. All animals were anesthetized by intraperitoneal injection of ketamine (75 mg/kg) and xylazine (12 mg/kg).

Nerve conduction studies

Monopolar needles were used for stimulation and disc electrodes were used for recording. To demonstrate the conduction parameters of two different fibers of tibial nerve, stimulation was performed on a proximal (Ischiatic notch) and a distal (Popliteal fossa) sites and recording were taken from a distal (Foot intrinsic muscles) and a proximal (Gastrocnemius) muscle [Figure 1]. As the only parameter which is properly expected to demonstrate the difference was the conduction velocities, the conduction velocities were recorded according to the study protocol. Recording sensitivity was 5 mv/division and 500 mcV/division. The distances were calculated as millimeters.
The EMG was repeated on the 1th, 2nd and the 3rd month.

Statistics

All rats' glucose levels and ES data were uploaded to SPSS 16.0 and for the statistical analyses; Wilcoxon and Mann Whitney U tests were performed.

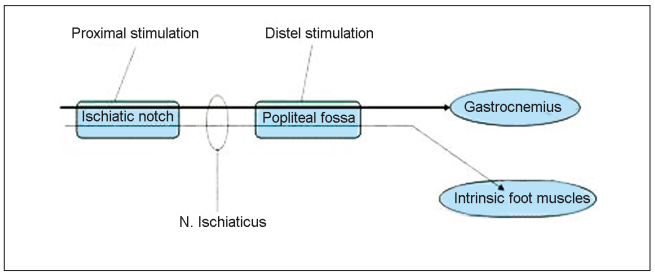

Figure 1: Design of the study(stimulation and recording sites)

Results

Control group

Blood glucose values of the day 0, 1st, 2nd and 3rd month values of proximal and distal recorded conduction velocities were linearly self-analyzed. There was no significant difference between the values of 0th day, 1st, 2nd and 3rd months. But proximal recorded conduction velocities (52.4 ± 4.1 meter/second) were higher than the distal recorded conduction velocities (45.7 ± 3.9 meter/second). The difference was statistically significant ($P = 0.018$) [Figure 2].

Streptozotocine group

Blood glucose, proximal and distal conduction velocities of the day 0 were compared with the control group. There was no significant reflecting that both groups had similar aspects. All rats had blood glucose levels higher than 300 mg/dL at the 10th day [Figure 3]. The mean conduction velocities recorded from gastrocnemius were significantly faster than the distal recorded ones for all months ($P = 0{,}032$ for the day 0, 0,028 for the 1st, 0,016 for the 2nd and 0.028 for the 3rd months). Both proximal and distal conduction velocities significantly decreased during the time (1st, 2nd and 3rd month) [Figure 4].

Proximal and distal recorded conduction velocities (Control group versus Streptozotocine group) were compared and the difference of the 3rd month's values was statistically significant (Proximal conduction velocities; $P = 0.020$, distal conduction velocities; $P = 0.039$).

The decrement percentage observed in the proximal recorded conduction velocities was similar to the decrement recorded in distal site ($P = 0.352$).

Discussion

In this study we found a significant difference between the proximal and distal recorded conduction velocity values. This result supported that the method we used successfully demonstrated the different properties of nerve fiber groups even they are in the same nerve segment.

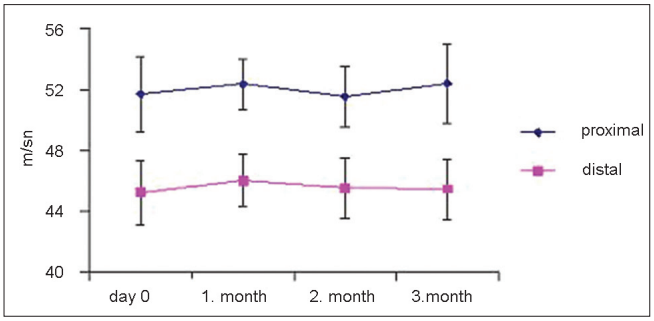

Figure 2: Control group's conduction velocities for both distal and proximal recording sites

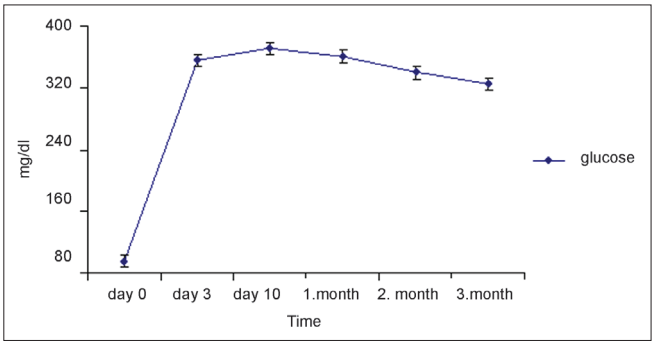

Figure 3: Glucose levels of the STZ group

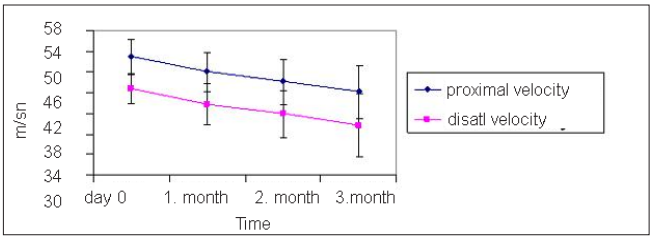

Figure 4: Change of proximal and distal conduction velocities in STZ group

In our recent study,[9] designed to compare the recording techniques in rats, we found that the conduction velocities of the nerve fiber groups innervating proximal muscles were higher than the nerve fibers innervating distal ones. Although the sciatic nerve was stimulated between the same sites, the conduction velocity recorded from the gastrocnemius muscle was faster than the one recorded from the intrinsic foot muscles. This result suggests that the nerve fiber groups innervating gastrocnemius muscle are relatively larger and faster than the fibers innervating intrinsic foot muscles.

Conduction parameters of nerve fibers with different diameters are frequently studied in different peripheral nerves, but our study is the only study evaluating conduction velocities of the different fiber groups in the same peripheral nerve segment, in rats. Gassel and Trojaborg did use the same technique for the same purpose in humans.[10]

In the development of neuropathic process: Metabolic, vascular, neurotrophic and immunologic factors are considered to be affected by hyperglycemia, causing degeneration of axons and myelin.[11] In diabetic neuropathy, the level of damage to the nerve fibers is directly associated with the duration and the severity of hyperglycemia. Furthermore, diabetes also affects both large-and small-diameter nerve fibers over the same period of time.[12] In the present study hyperglycemia caused a similar decrease in both distal and proximal conduction velocities. Our method successfully demonstrated the conduction parameters of different nerve fiber groups. But the process seemed to be homogeneous in both sites. The relatively large and the small nerve fiber groups of the same nerve segment were similarly affected by the hyperglycemia. These findings indicate that proximal and distal segments of peripheral nerves are affected equally in the early stages of experimental diabetic neuropathy. This may be caused by the short term follow up period due to the life expactancy of rats. Future studies may be designed in human subjects who had the diagnosis of diabetes for longer periods.

As a result, the difference between the conduction velocities which were calculated from distally and proximally recorded compound muscle potential responses reflects the diameter of nerve fiber groups innervating different muscles. Our method which allowed us to record the parameters of two different nerve fibers with only two stimulations is seem to be was successful to demonstrate this difference. If the classical methods were used we would have to administrate four stimulations to evaluate two different nerve fibers, so adaptation of this method to human electrophysiological studies would be helpful in clinical practice. But our method did not enhance any advantage to standard techniques. This may particularly be caused by the follow up period of our study. Small differences might be relevant in the later stages of developing neuropathy.

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