Streptozotocin-induced Diabetes Causes Crucial Morphological Changes in Abdominal Motoneurons and Muscles of Rats

Naomi Oshiro1, Ken Muramatsu1, Toru Tamaki1, Masatoshi Niwa1 *
1Department of Occupational Therapy, Kyorin University, Tokyo, Japan
2Department of Physical Therapy, Kyorin University, Tokyo, Japan
3Department of Physical Therapy, Health Science University, Yamanashi, Japan

Abstract

Background: Diabetic neuropathy (DN) is a major complication of diabetes. Although it is well-established that DN targets sensory and autonomic nerves, little is known about its influence on motor disorders.

Methods: This study investigated morphological alterations in abdominal (Abd) motoneurons and muscles of experimental type 1 diabetic rats. Alterations in the number and size of Abd motoneurons were studied using retrograde labeling techniques in diabetic rats 6 or 14 weeks after injection of streptozotocin (diabetic group). Age-matched control animals were labeled at 6 or 14 weeks after saline injection (control group). Further, the thicknesses of the external oblique, internal oblique, transversus abdominis (TA), and rectus abdominis muscles were similarly examined and the cross-sectional area of the TA myocytes was measured.

Results: The number and mean size of cell bodies significantly decreased in Abd motoneurons in the diabetic group compared with the control group (P < 0.05). As diabetes progressed, there was a clear decrease in the number and mean motoneuron size (P < 0.05). In the diabetic group, the thickness of Abd muscles was reduced, as was the cross-sectional area of the TA myocytes (P < 0.05). Moreover, there was a clear decrease in muscle thickness and in the cross-sectional area of the myocytes (P < 0.05).

Conclusion: We suggest that hyperglycemia induced a reduction in the number and size of Abd motoneurons and atrophy of Abd muscles at 6 and 14 weeks after induction of diabetes by streptozotocin. Therefore, Abd muscular disorders caused by hyperglycemia may relate to a wide range of disorders, such as those involved with expiratory, defecation function, and trunk movement.

Introduction

Diabetic neuropathy (DN) is symmetric and duration dependent, and involves sensory loss, pain, and distal weakness in the early stage of diabetes [1-3]. However, in the later stage, muscle weakness spreads through proximal areas, including ankles, knees, and hips, whereas "stocking and glove" sensory losses remain restricted to distal regions [4,5]. These weaknesses also correlate highly with the severity of DN[5,6]. However, we recently revealed a significant decrease in the number of labeled gamma motoneurons [7] and a loss of labeled alpha motoneurons in medial gastrocnemius (MG) muscles, followed by a later loss of labeled gamma motoneurons in MG muscles using retrograde labeling technique [8]. Our finding will help in elucidating the mechanism of motor disturbance of diabetic patient. However, to date, there is no information available on how diabetes affects the motoneurons other than hindlimb motor nuclei.

Abdominal (Abd) muscles consist of the external oblique (EO), internal oblique (IO), transversus abdominis (TA), and rectus abdominis (RA), which are innervated by motoneurons located in the ventral horn of the lower thoracic and upper lumbar spinal cord [9,10]. Abd muscles play an important role in posture and walking [11-13]; vomiting [14]; and respiration, particularly the control of expiration [15-17], and excretion movements, such as defecation and urination [15,18]. Therefore, functional decline in Abd muscles due to DN is expected and included in various dysfunctions. However, there is no information about how diabetes affects Abd motoneurons and muscles, although Abd muscles play such an important role.

We used streptozotocin (STZ) to induce experimental type 1 diabetes in rats and examined anatomical alterations in motoneurons in Abd motor nuclei by using retrograde-labeling techniques. In addition, we performed morphological examination of Abd muscles.

*Corresponding Author: Prof. Masatoshi Niwa, Department of Occupational Therapy, Kyorin University, Tokyo, Japan, 5-4-1 Shimorenjaku, Mitaka, Tokyo 181-8612, Japan, Tel: +81-422-47-8000, Fax:+81-422-47-8077; E-mail: mt-niwa@ka.kyorin-u.ac.jp


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Materials & Methods

All animal experiments were performed in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publication No. 8023, revised 1978). All the experimental procedures were approved by the Animal Ethics Committee of Kyorin University.

Forty-two 13-week-old male Wistar rats (purchased from Sankyo Labo Service Corporation, Inc., Tokyo, Japan) were used in this experiment. Type 1 diabetes was induced by administration of STZ (100 mg/kg in saline; i.p.) in 22 animals. Plasma glucose was determined to confirm the diabetic status. Twenty age-matched control animals were used for the control of the experiment. Type 1 diabetes was induced by administration of streptozotocin (100 mg/kg in saline; i.p.) and perfused transcardially with 500–1000 mL of normal saline containing heparin sodium, followed by 4% paraformaldehyde in 0.1 M phosphate buffer at 4°C. The T8 to L2 portion of the spinal cord was removed and placed in cold fixative (4% paraformaldehyde) for 24 hours. The T8 to L2 portion of the segment was sectioned serially on a vibratome (longitudinal 80-μm-thick sections). These sections were mounted on glass slides and examined through fluorescence microscopy. Microscope images were photographed by using a digital camera (BX-50, OLYMPUS, Tokyo, Japan). The numbers of motoneurons and diameters of the soma in the digital images were measured using Image J (NIH, Bethesda, MD, USA). We calculated the average soma diameter (half of the sum of the maximum and minimum diameters of the ovals) in Abd cell bodies.

Measurements of motoneurons

At 4 weeks or 12 weeks after STZ or saline injection, the diabetic and age-matched control animals were used for measurements of muscles. All animals were anesthetized with 4% halothane at the induction of anesthesia and maintained with inhalation halothane at 1%. Rectal temperature was maintained at 37-38°C by using a heating pad. Under aseptic conditions, the ventral branch of the 13th thoracic spinal cord (T13) nerve and the first lumbar spinal cord (L1) nerve were dissected from Abd muscles, and the central cut ends of T13 and L1 nerves were dipped, ☐;three portions along the Th13 and L1 nerves sampled. L; lumbar nerve, T; thoracic nerve, EO; M. obliquus abdominis externus, LD; M. lattissimus dorsi, RA; M. rectus abdominis, O; central cut ends of nerves dipped, ☐;three portions along the Th13 and L1 nerves sampled.

After a survival period of 2 weeks, the animals were re-anesthetized with pentobarbital (35 mg/kg; i.p.) and perfused transcardially with 500–1000 mL of normal saline containing heparin sodium, followed by 4% paraformaldehyde in 0.1 M phosphate buffer at 4°C. The T8 to L2 portion of the spinal cord was removed and placed in cold fixative (4% paraformaldehyde) for 24 hours. Next, the 8th thoracic spinal segment through the 2nd lumbar spinal segment was sectioned serially on a vibratome (longitudinal 80-μm-thick sections). These sections were mounted on glass slides and examined through fluorescence microscopy. Microscope images were photographed by using a digital camera (BX-50, OLYMPUS, Tokyo, Japan). The numbers of motoneurons and diameters of the soma in the digital images were measured using Image J (NIH, Bethesda, MD, USA). We calculated the average soma diameter (half of the sum of the maximum and minimum diameters of the ovals) in Abd cell bodies.

Measurements of muscle thickness and myocytes

At 6 weeks or 14 weeks after STZ or saline injection, the diabetic and age-matched control animals were used for measurements of muscles. To examine the degree of muscle atrophy of Abd muscles, histological analysis was conducted on EO, IO, TA, and RA muscles. We used Abd muscles innervated by the Th13 and L1 nerves. The Th13 nerve innervates the upper portion of Abd muscles containing EO, IO, TA, and RA muscles, and the L1 nerve innervates the lower portion of Abd muscles containing EO, IO, and TA muscles (Figure 1).

The animals were anesthetized by pentobarbital (35 mg/kg; i.p.) and euthanized by an overdose of pentobarbital (50 mg/kg; i.p.), and the Abd muscles were removed. Three muscle samples were collected along the Th13 and L1 nerves (Figure 1). A transverse section of each frozen portion was cut at 10 μm thickness. For the histological analysis, sections were stained with hematoxylin-eosin. Every muscle thickness performed four muscle layers (EO, IO, TA, and RA) were measured at three points for every 1 mm, and those means were used for analysis. We also measured the fiber area because the TA could be cut from the belly of the muscle perpendicularly. We measured the mean cross-sectional area of 50 muscle cells and counted the nuclei of the muscle cells.
Data analysis

Significance differences were evaluated by using independent t-tests using SPSS software (version 23, IBM, Armonk, USA). Differences of P < 0.05 were considered statistically significant.

Results

Measurements of Abd Motoneurons

Both diabetic animals (6 weeks after induction of diabetes; 6WD, n = 5, and 14 weeks after induction of diabetes; 14WD, n = 5) and control animals (6 weeks after saline injection; 6WC, n = 5, and 14 weeks after saline injection; 14WC, n = 5) were used for analysis (Table 1).

As shown in Figure 2, all the retrogradely labeled motoneurons were clearly identifiable by their cell bodies and dendrites and were located in the ventral horn of the spinal cord. Table 1 shows the total number and the average soma diameters of the Abd motoneurons. There was a decrease in the total number of Abd motoneurons in the diabetic group (78.1% in T13 and 66.8% in L1 of 6WD, 81.4% in T13 and 72% in L1 of 14WD). The total number of Abd motoneurons in L1 was significantly reduced in diabetic animals compared to control animals.

Figure 3 shows a frequency histogram of the average soma diameters of Abd motoneurons in each experimental group. The distributions of Abd motoneurons were unimodal. Some large motoneurons appeared to be missing in all histograms of the diabetic animals compared to control animals.

Measurements of Abd Muscle Thickness and Myocytes

The diabetic animals (6WD, n = 6, and 14WD, n = 6) and the control animals (6WC, n = 4, and 14WC, n = 6) were used for analysis (Table 2).

To examine the degree of muscle atrophy of Abd muscles, every muscle thickness per four muscle layers (EO, IO, TA, and RA) was measured at three points for every 1 mm and those means were used for analysis. Macroscopically, the muscle layer in the diabetic groups appeared as a thin film as if it had no muscular tissue and there was a clear decrease in the muscle thicknesses per muscle layer in the diabetic group. There was a significant difference in Abd muscles, except RA muscle, between 6WC and 6WD animals, and in all Abd muscles between 14WC and 14WD animals (Table 2). In particular, the muscle with the greatest rate of change was TA muscle, and its thickness decreased by half in T13 and L1, respectively. Moreover, there was a significant difference in EO, IO, and TA muscles in T13, and in TA in L1 between 6WD and 14WD animals. Thus, as diabetes progressed, there was a clear decrease in the muscle thicknesses.

To examine the morphological alterations in Abd muscles, the cross-sectional area of 50 myocytes in TA muscle were measured and those means were used for analysis. Because Abd muscle was thin in the diabetic animals, it was only possible to count a maximum of 50 cells. Next the numbers of the nuclei in the myocytes were counted. The mean cross-sectional areas of TA in diabetic animals were obviously smaller than those in control animals, whereas the numbers of the myocyte nuclei were not significantly different. The mean cross-sectional areas of 14WC had grown larger bigger than those of 6WC animals. When we adjusted for body weight, there was a significant difference in L1 between 6WC and 6WD animals and in both T13 and L1 between 14WC and 14WD animals (Table 2). Briefly, there was a significant difference between 6WD and 14WD animals. As diabetes progressed, a clear decrease was observed in mean cross-sectional areas (Figure 5).

Figure 2: Representative images of retrogradely labeled Abd motoneurons in horizontal sections.
Figure 3: Distribution of the soma diameters of Abd motoneurons.
A: size distribution of T13 in 6WC and 6WD. B: size distribution of L1 in 6WC and 6WD. C: size distribution of T13 in 14WC and 14WD. D: size distribution of L1 in 14WC and 14WD. 6WD: animals 6 weeks after induction of diabetes, 14WD: animals 14 weeks after induction of diabetes, 6WC: control animals 6 weeks after injection of saline, 14WC: control animals 14 weeks after injection of saline, T13: 13th thoracic spinal cord, L1: 1st lumbar spinal cord.
The vertical axis shows the number of cells, and the horizontal axis shows average diameter. Control: ■, Diabetes: ○. Overlap area of controls with diabetic animals are indicated in gray.

Figure 4: Representative spatial distribution of Abd motoneurons in horizontal sections.
A: 6W animals, a: spatial distribution in a control animal, b: spatial distribution in a diabetic animal. B: 14W animals, a: spatial distribution in a control animal, b: spatial distribution in a diabetic animal. •: labeled cell bodies labeled by the T13 nerve, ○: labeled cell bodies labeled by the L1 nerve. Bar=100μm.
### Table 1: Numbers and average diameters of Abd motoneurons.

<table>
<thead>
<tr>
<th>Rat. No</th>
<th>Control No. 6WC (327.6–357.5 g, 142.8±18.6 mg/dL)</th>
<th>Control No. 14WC (379.6–434.0 g, 162.4±24.3 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>T13</strong></td>
<td><strong>L1</strong></td>
</tr>
<tr>
<td>No. 1</td>
<td>262</td>
<td>36.8 (±8.0)</td>
</tr>
<tr>
<td>No. 2</td>
<td>266</td>
<td>39.5 (±8.2)</td>
</tr>
<tr>
<td>No. 3</td>
<td>289</td>
<td>41.8 (±8.2)</td>
</tr>
<tr>
<td>No. 4</td>
<td>298</td>
<td>43.6 (±8.4)</td>
</tr>
<tr>
<td>No. 5</td>
<td>300</td>
<td>40.1 (±7.9)</td>
</tr>
<tr>
<td>Mean</td>
<td>283.0 (±17.9)</td>
<td>40.4 (±2.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rat. No</th>
<th>DM No. 6WD (175.2–227.0 g, 436.6±40.7 mg/dl)</th>
<th>DM No. 14WD (140.6–188.0 g, 478.0±51.9 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>T13</strong></td>
<td><strong>L1</strong></td>
</tr>
<tr>
<td>No. 1</td>
<td>173</td>
<td>35.5 (±5.2)</td>
</tr>
<tr>
<td>No. 2</td>
<td>174</td>
<td>37.7 (±6.3)</td>
</tr>
<tr>
<td>No. 3</td>
<td>161</td>
<td>36.0 (±8.2)</td>
</tr>
<tr>
<td>No. 4</td>
<td>304</td>
<td>39.6 (±7.6)</td>
</tr>
<tr>
<td>No. 5</td>
<td>293</td>
<td>34.9 (±7.3)</td>
</tr>
<tr>
<td>Mean</td>
<td>221.0 (±71.0)</td>
<td>36.7 (±1.9)</td>
</tr>
</tbody>
</table>

### Table 2: Thicknesses and Myocytes and Nucleus number of type the muscle in each area.

<table>
<thead>
<tr>
<th>Control</th>
<th>6WC (N=4, 334.1–370.7 g, 159.3±32.8 mg/dl)</th>
<th>14WC (N=6, 381.5–468.4 g, 171.8±27.3 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>T13</strong></td>
<td><strong>L1</strong></td>
</tr>
<tr>
<td>EO</td>
<td>(Mean ± SD mm) Layer</td>
<td>0.80 (±0.13)</td>
</tr>
<tr>
<td>IO</td>
<td>0.88 (±0.14)</td>
<td>0.92 (±0.19)</td>
</tr>
<tr>
<td>TA</td>
<td>0.73 (±0.08)</td>
<td>0.87 (±0.05)</td>
</tr>
<tr>
<td>RA</td>
<td>2.12 (±0.64)</td>
<td>2.31 (±0.69)</td>
</tr>
<tr>
<td>TA</td>
<td>Myocytes (μm²)</td>
<td>4047.1 (±693.3)</td>
</tr>
<tr>
<td>Myocytes (μm²/weight)</td>
<td>11.2 (±1.7)</td>
<td>12.1 (±2.5)</td>
</tr>
<tr>
<td>Number of nucleus</td>
<td>137.5 (±14.8)</td>
<td>150.5 (±35.3)</td>
</tr>
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<table>
<thead>
<tr>
<th>DM</th>
<th>6WD (N=6,184.1–237.2 g, 479.0±70.5 mg/dl)</th>
<th>14WD (N=6,140.6–187.6 g, 506.8±62.3 mg/dl)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>T13</strong></td>
<td><strong>L1</strong></td>
</tr>
<tr>
<td>EO</td>
<td>(Mean ± SD mm) Layer</td>
<td>0.43 (±0.08)*</td>
</tr>
<tr>
<td>IO</td>
<td>0.52 (±0.06)*</td>
<td>0.63 (±0.11)*</td>
</tr>
<tr>
<td>TA</td>
<td>0.57 (±0.11)*</td>
<td>0.52 (±0.11)*</td>
</tr>
<tr>
<td>RA</td>
<td>1.79 (±0.60)</td>
<td>1.42 (±0.46)*</td>
</tr>
<tr>
<td>TA</td>
<td>Myocytes (μm²)</td>
<td>2003.8 (±368.2)*</td>
</tr>
<tr>
<td>Myocytes (μm²/weight)</td>
<td>9.3 (±0.7)</td>
<td>8.6 (±1.3)*</td>
</tr>
<tr>
<td>Number of nucleus</td>
<td>118.7 (±13.2)</td>
<td>119.0 (±8.5)</td>
</tr>
</tbody>
</table>

Table 1: Numbers and average diameters of Abd motoneurons.

DM: diabetes mellitus, No: number (Average body weight and average blood glucose concentrations).

Data represented as mean ± SD: * represents = P < 0.05 (compared with control animals).

Table 2: Thicknesses and Myocytes and Nucleus number of type the muscle in each area.


Data represented as mean ± SD: * represents = P < 0.05 (compared with control animals).
motoneurons. Data suggest that Abd muscles were innervated by alpha and gamma motor fibers. Therefore, anatomical and physiological studies have shown that Abd alpha and gamma motor fibers exhibited the expiratory activity, in response to positive air pressure [17].

It is known that positive air pressure corresponds to gamma motor fibers, although size distribution of Abd motor fibers in peripheral nerves showed a unimodal distribution. This was different from hindlimb motoneurons whose size showed bi-modal distributions, in that small groups corresponded to gamma motoneurons and large groups to alpha motoneurons [8, 10]. However, this difference does not mean that Abd motoneurons do not have gamma motoneurons. Because it was previously reported that large (presumed alpha) and small gamma motoneurons of the MG nuclei had smaller cross-sectional areas (12 weeks after STZ injection) and were fewer in number (12 and 24 weeks after STZ injection) [8]. In this study, however, we revealed that only 6 weeks of diabetes induced the loss of Abd motoneurons. Since there is no data of hind-limb motoneurons after 6 weeks following induction of diabetes, it cannot be compared, but Abd motoneurons are considered to be similarly damaged by hyperglycemia.

As shown in Figure 3, size of Abd motoneurons showed unimodal distribution. This was different from hindlimb motoneurons whose size showed bi-modal distributions, in that small groups corresponded to gamma motoneurons and large groups to alpha motoneurons [8, 10]. However, this difference does not mean that Abd motoneurons do not have gamma motoneurons. Because it was previously reported that size distribution of Abd motor fibers in peripheral nerves showed a bi-modal distribution and it is very likely that the large motor fibers corresponded to alpha motor fibers and the small motor fibers corresponded to gamma motor fibers, although size distribution of Abd cell bodies showed uni-modal [10]. It also known when positive pressure was imposed at the end-expiratory line, Abd alpha and gamma motor fibers exhibited the expiratory activity, in response to the positive air pressure [17]. Therefore, anatomical and physiological data suggest that Abd muscles were innervated by alpha and gamma motoneurons.

In this study, the number and mean size of cell bodies decreased in Abd motoneurons in the diabetic group. Additionally, size distribution of Abd motoneurons showed a decrease of the number of larger motoneurons (Figure 3). At first glance, the main component of these alterations seems to be occurred by a loss of larger alpha motoneurons. However, our previous report indicated that the diabetes predominantly induces loss of gamma motoneurons innervating MG muscle spindles [7]. Alteration of size distribution may cause by shrinkage of the cell bodies of larger alpha motoneurons and loss of smaller gamma motoneurons.

## Abd Muscles

There was a clear decrease in the muscle thicknesses in the diabetic group. The thickness of each muscle was almost halved between that of 14WC and 14WD animals. Therefore, the functional decline in Abd muscles will appear to be remarkable with diabetes. The sizes of myocytes in TA muscle decreased in the diabetic animals. The thinning of Abd muscles might have little or no relationship to decrease of the number of motoneurons and there were few angulated fibers in the diabetic animals, which were characteristic of neurogenic muscle atrophy. Compared to a decrease in the number of motoneurons, thinning of the muscle was remarkable (Abd muscles which were innervated by motoneurons in the T13 segment decreased in thickness without significant loss of motoneurons). This discrepancy of the number of Abd motoneurons and atrophy of Abd muscles suggests that muscle thinning might be caused by lack of nutritional supply due to peripheral vascular injury, etc. It is known that if denervation progresses slowly, muscle will not show typical degeneration atrophy because preserved motoneurons are given time to re-innervate muscle fibers. It also suggests that loss of Abd motoneurons might occur on gamma motoneurons which innervate intra-fusal fiber of muscle spindle. Therefore, it was not related to thinning of the muscle.

### Discussion

## Abd Motoneurons

In a previous paper, we discussed the possibility that decreased labelling of motoneurons may not be caused by technical problems with retrograde labeling [7, 19-22]. In this study, we revealed an aspect of diabetes pathology in Abd motoneurons. We previously found that both size and number of presumed gamma motoneurons were reduced (22 weeks after STZ injection) in rats [7] but later reported that large (presumed alpha) and small gamma motoneurons of the MG nuclei had smaller cross-sectional areas (12 weeks after STZ injection) and were fewer in number (12 and 24 weeks after STZ injection) [8]. In this study, however, we revealed that only 6 weeks of diabetes induced the loss of Abd motoneurons. Since there is no data of hind-limb motoneurons after 6 weeks following induction of diabetes, it cannot be compared, but Abd motoneurons are considered to be similarly damaged by hyperglycemia.

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It might seem to be natural to conclude that diabetes targets the gamma motoneurons innervating the distal muscles of the hindlimb by which MG gamma motoneurons are injured, while biceps femoris motoneurons are preserved [8]. This might reflect the characteristic of DN featuring length-dependent peripheral nerve disorders referred to as “stocking and glove” signs and symptoms. However, it is unclear why Abd muscles, which are not innervated by long peripheral nerves, are damaged severely. A study of rat leg muscles indicated that fast-twitch skeletal muscle fibers are more dependent on insulin for maintenance of their normal metabolic and morphological characteristics than slow-twitch fibers [23], and that fast-twitch muscles undergo profound wasting and decreased strength [24]. Furthermore, the isomyosins of slow-twitch oxidative myofibers are more resistant to hormonal and metabolic disorders during diabetes than the isomyosins of fast-twitch fibers [25]. Abd muscles of rats might have a large number of fast-twitch fibers, or Abd muscles might have been severely injured in the diabetic group due to the basic structural differences from lower limbs.

Patients with type 1 diabetes mellitus have been shown to have a significantly lower than normal total lung capacity, residual volume, and forced vital capacity [26]. This suggests that a restrictive type of lung disease can be caused by an intrinsic lung-tissue derangement as well as pulmonary microangiopathy [26]. Moreover, some of these causes may result in dysfunction of Abd muscles because they contribute to increases in intra-abdominal pressure [18]. Loss of Abd motoneurons and decrease in Abd muscle thickness were observed after induction of diabetes by streptozotocin. Therefore, Abd muscular disorders would be related to a wide range of disorders such as those involved with expiratory, defecation function, and trunk movement. We would like to examine the mechanisms of the disorders referred to as “stocking and glove” signs and symptoms. This study investigated morphological alterations in Abd motoneurons and muscles of experimental type I diabetic rats. The number and mean size of cell bodies decreased in Abd motoneurons in the diabetic group. There was a clear decrease in muscle thickness and in the cross-sectional area of the myocytes in the diabetic group. We suggest that the hyperglycemia could induce the reduction of number and size of Abd motoneurons and the atrophy of Abd muscles. Those were observed at 6 and 14 weeks after induction of diabetes by streptozotocin. Therefore, Abd muscular disorders caused by the hyperglycemia would relate to a wide range of disorders such as those involved with expiratory, defecation function, and trunk movement.

Conclusions

This study investigated morphological alterations in Abd motoneurons and muscles of experimental type I diabetic rats. The number and mean size of cell bodies decreased in Abd motoneurons in the diabetic group. There was a clear decrease in muscle thickness and in the cross-sectional area of the myocytes in the diabetic group. We suggest that the hyperglycemia could induce the reduction of number and size of Abd motoneurons and the atrophy of Abd muscles. Those were observed at 6 and 14 weeks after induction of diabetes by streptozotocin. Therefore, Abd muscular disorders caused by the hyperglycemia would relate to a wide range of disorders such as those involved with expiratory, defecation function, and trunk movement.

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Competing Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

NO performed all the described experiments.

NO and MN designed the study, analyzed, and evaluated the data and authored the manuscript.

All co-authors participated in data collection and analysis and have read and approved the final manuscript.

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