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Research report

Effect of streptozotocin-induced diabetes on motor representations in the motor cortex and corticospinal tract in rats

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ABSTRACT

Motor disorders in patients with diabetes are associated with diabetic peripheral neuropathy, which can lead to symptoms such as lower extremity weakness. However, it is unclear whether central motor system disorders can disrupt motor function in patients with diabetes. In a streptozotocin-induced rat model of type 1 diabetes, we used intracortical microstimulation to evaluate motor representations in the motor cortex, recorded antidromic motor cortex responses to spinal cord stimulation to evaluate the function of corticospinal tract (CST) axons, and used retrograde labeling to evaluate morphological alterations of CST neurons. The diabetic rats exhibited size reductions in the hindlimb area at 4 weeks and in trunk and forelimb areas after 13 weeks, with the hindlimb and trunk area reductions being the most severe. Other areas were unaffected. Additionally, we observed reduced antidromic responses in CST neurons with axons projecting to lumbar spinal segments (CST-L) but not in those with axons projecting to cervical segments (CST-C). This was consistent with the observation that retrograde-labeled CST-L neurons were decreased in number following tracer injection into the spinal cord in diabetic animals but that CST-C neurons were preserved. These results show that diabetes disrupts the CST system components controlling hindlimb and trunk movement. This disruption may contribute to lower extremity weakness in patients.

1. Introduction

Diabetic neuropathy (DN), which damages both somatic and autonomic nerves, is a major complication in diabetes (Dobretsov et al., 2007). The most common early clinical pattern for DN is symmetric and length-dependent and involves sensory losses and pain (Dyck and Giannini, 1996). Subsequent motor dysfunction leads to lower extremity weakness (Andersen, 2012), which is believed to be associated with reduced quality of life and mobility impairments such as an increased risk of falling, altered gait and balance, and increased body sway (Ijzerman et al., 2012; Petrofsky et al., 2005; Uccioli et al., 1995).

This muscle weakness is closely related to the signs and severity of DN (Andersen et al., 1996). Interestingly, lower extremity muscle weakness spreads through proximal areas including ankles, knees, and hips, whereas "stocking and glove" sensory losses occur within distal regions (Abadi et al., 2017; Andersen, 2012; Dobretsov et al., 2007). Magnetic resonance imaging (MRI) has revealed that muscle weakness occurs in parallel with muscular atrophy in the feet and lower extremities (Andersen et al., 1997, 2004). In diabetic animals, early-stage DN features reductions in motor axon conduction velocities, followed by decreased neuromuscular endplate innervation and motor unit enlargement (Francis et al., 2011; Ramji et al., 2007). These effects are observed in motoneurons innervating the animals' distal hindlimb muscles but not in those innervating proximal hindlimb muscles (Muramatsu et al., 2017), which suggests that muscle atrophy and weakness in the feet and lower extremities results from

Abbreviations: 4WC, control animals at 4 weeks after sham diabetes induction; 4WD, diabetic animals at 4 weeks after diabetes induction; 13WC, control animals at 13 weeks after sham diabetes induction; 13WD, diabetic animals at 13 weeks after diabetes induction; 23WC, control animals at 23 weeks after sham diabetes induction; 23WD, diabetic animals at 23 weeks after diabetes induction; CNS, central nervous system; CST, corticospinal tract; CST-C, CST neurons projecting axons to cervical spinal cord segments; CST-L, CST neurons projecting axons to lumbar spinal cord segments; DN, diabetic neuropathy; DTR, dextran-Texas Red tracer; MNCV, motor NCV; NCV, nerve conduction velocity; SNCV, sensory NCV; STZ, streptozotocin.

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denervation. However, proximal hindlimb muscles differ from distal ones in important ways. For example, despite older adults with type 2 diabetes having greater lower extremity muscle mass than those without diabetes do, those with diabetes exhibit less knee extendability than those without do (Park et al., 2006). This characteristic muscle weakness is thought to be associated with increased intramuscular noncontractile tissue (Tuttle et al., 2011). Thus, in addition to DN, diabetes itself may reduce lower striated muscle strength around the knee (Park et al., 2006).

While peripheral motor nerve and muscle disorders in diabetes are well described, fewer studies have examined the effects of diabetes on the central motor system, despite the well-documented fact that diabetes affects the central nervous system (CNS) (Allen et al., 2004; Biessels et al., 1999; Hernández-Fonseca and Rincón, 2009; Weinger and Jacobson, 1998). The corticospinal tract (CST) is an essential descending pathway for voluntary movement generation. It originates in the motor cortex and directly connects to the spinal cord (Lemon, 2008). A few clinical studies suggest that diabetes also affects the CST. For example, patients with insulin-dependent diabetes exhibit impaired excitability of upper extremity cortical motor areas, and MRI studies have revealed lower axial diffusivity and white matter volumes, including CST volumes, in patients with type 2 diabetes (Andersen et al., 1995; Barnea-Goraly et al., 2014). Moreover, animal experiments have revealed size reductions in the forelimb motor cortical area in early-stage diabetes (Emerick et al., 2005). However, little is known about alterations of the CST system for the lower extremities, despite diabetes-induced motor disorders predominantly affecting the lower extremities (Park et al., 2006). The only available information comes from motor-evoked potential studies that reported prolonged central motor conduction times in lower extremity muscles (Abbruzzese et al., 1993; Goldenberg et al., 2004).

We therefore examined the alterations in cortical motor area representations of the hindlimb and trunk in a streptozotocin (STZ)-induced animal model of type 1 diabetes. We also compared diabetes-induced electrophysiological and morphological alterations in CST neurons projecting to the cervical spinal segment, which controls upper limb movement, to those in neurons projecting to the lumbar spinal segment, which controls hindlimb and trunk movement.

2. Results

2.1. The effects of diabetes on body weight, blood glucose, and urine ketoacids

Compared to the control animals, the diabetic rats exhibited hyperglycemia and reduced body weights. They also exhibited blood glucose levels of approximately 400 mg/dl within 2–3 days of STZ injection and for the remainder of the study. The control and diabetic animals both exhibited body weights of 289–329 g prior to the STZ or saline injections, but the body weights of control group rats at 23 weeks after saline injections (23WC) increased to approximately 400 g, whereas the body weights of diabetic rats at 23 weeks after model induction (23WD) decreased to approximately 200 g. We did not observe urine ketoacids in either group (Tables 1, 3, and 4).

2.2. Alteration of cortical motor areas and nerve conduction velocities (NCVs)

Typical low-threshold stimulation maps of motor cortices in 4WC, 4WD, 13WC, 13WD, 23WC, and 23WD rats are shown in Fig. 1A–F. There was little variation in the cortical motor areas' arrangements and shapes. In most animals, the vibrissa and neck areas divided the forelimb area into rostral and caudal portions, but in several animals from both the control and diabetic groups, the rostral and caudal areas were fused and barely distinguishable. We therefore combined both areas for analysis. We also could not observe the internal organization of the forelimb, trunk, and hindlimb areas.

The hindlimb, forelimb, and trunk motor areas were smaller in the diabetic rats than in the control rats (Fig. 1G). This was especially true of the hindlimb and trunk areas. Relative to timepoint-matched controls, the diabetic rats exhibited significantly smaller hindlimb areas at 4 weeks (69.4% of the timepoint-matched controls' areas, $P < .0001$), 13 weeks (56.3%, $P < .0001$), and 23 weeks (39.2%, $P < .0001$). The diabetic rats' trunk areas were not significantly smaller at 4 weeks (62.6%, $P = .16$), but they were significantly smaller at 13 weeks (43.3%, $P = .032$) and 23 weeks (7.9%, $P < .0001$). The effects on the forelimb area

Table 1
Body weights, blood glucose levels, urine ketoacids and conduction velocities at different timepoints in animals used for intracortical microstimulation experiments. Abbreviations: MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

	4 W			13 W			23 W		
	Control (n = 6)	Diabetic (n = 6)	P value	Control (n = 6)	Diabetic (n = 6)	P value	Control (n = 6)	Diabetic (n = 6)	P value
Body weight (g)	297.0 ± 18.2	243.6 ± 15.8	0.0031	377.2 ± 25.0	206.2 ± 33.9	<.0001	432.2 ± 33.8	175.2 ± 9.9	<.0001
Blood sugar (mg/dl)	136.7 ± 6.1	395.2 ± 40.5	< 0.0001	135.2 ± 9.0	405.4 ± 34.1	<.0001	130.0 ± 17.1	384.5 ± 32.3	<.0001
Urine ketoacids	–	–		–	–		–	–	
MNCV (m/s)	55.3 ± 7.7	53.0 ± 5.4	0.9429	59.5 ± 10.1	45.4 ± 8.0	.0148	60.6 ± 5.2	41.8 ± 10.4	.001
SNCV (m/s)	44.9 ± 7.4	41.0 ± 7.8	0.5829	44.9 ± 5.2	36.2 ± 4.5	.0422	46.7 ± 4.1	35.9 ± 4.3	.0088

Table 2
Cerebral cortex current thresholds for evoked movements.

Type of movement	4 Weeks			13 Weeks			23 Weeks		
	Control (n = 6)	Diabetic (n = 6)	P value	Control (n = 6)	Diabetic (n = 6)	P value	Control (n = 6)	Diabetic(n = 6)	P value
Forelimb	19.0 ± 2.1	23.2 ± 1.4	0.0586	21.1 ± 2.3	27.2 ± 5.6	.0539	23.5 ± 1.9	26.2 ± 2.9	.2057
Hindlimb	18.2 ± 1.6	23.1 ± 2.1	0.6311	24.7 ± 1.6	28.6 ± 11.9	.7081	23.1 ± 2.0	24.5 ± 5.2	.971
Trunk	43.3 ± 4.0	46.6 ± 2.4	0.3119	37.8 ± 2.2	48.6 ± 2.0	.0001	39.7 ± 3.7	47.5 ± 3.5	.0223
Vibrissa	23.8 ± 4.3	26.2 ± 3.2	0.6948	24.8 ± 4.0	28.0 ± 3.0	.5515	24.7 ± 6.3	29.7 ± 1.9	.1419
Neck	19.9 ± 4.7	19.7 ± 2.9	0.9999	19.9 ± 6.5	26.3 ± 7.2	.1533	23.0 ± 6.2	22.3 ± 4.0	.9973
Jaw	27.0 ± 2.4	31.3 ± 3.8	0.6248	24.2 ± 8.4	22.5 ± 5.1	.981	23.2 ± 4.8	29.9 ± 7.5	.28