Differential Regulation of BDNF by Electrical Stimulation in Rat Hindlimb Muscles

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Introduction

Electrical stimulation is often used to restore the motor function in paralytic patients, as well as to treat the pathologic condition in paralytic muscles. The general effect of electrical stimulation in a vital organ is an increase in metabolism (caused by a change from anaerobic to aerobic metabolism), and an increase blood flow, oxygen consumption, and glucose consumption [1]. Short-term effect of electrical stimulation in the neuromuscular junction might include an increase the number of receptors or release of neurotransmitters, and long-term effects may include promotion of new formation of neural circuits to achieve neural plasticity [2]. However, no study has yet determined the mechanism for the therapeutic effect of electrical stimulation in paralytic muscles. In this study, effects of electrical stimulation on the sciatic nerve in the expression of BDNF protein and its mRNA were investigated in the soleus and the medial gastrocnemius muscles of rats.

Methods

Seventy Sprague-Dawley rats weighing 200- 250 g were used. Experimental animals were divided into two groups: a control group without any electrical stimulation to the sciatic nerve, and an experimental group with electrical stimulation to the sciatic nerve. A teflon-coated stainless steel cuff electrode was implanted in the sciatic nerve in both groups. Three types of electrical stimulation, such as 1 ms, 40Hz for 30 min, 1 ms, 40Hz for 5 min, and 1 ms, 1Hz for 30 min, were applied by a 5 sec ON/OFF stimulator, and the intensity of stimulation was 1- 3 V in all stimulus groups. BDNF protein was quantified using an enzyme-linked immunoassay (ELISA) and mRNA was measured by isolation of total cellular RNA in the soleus and the medial gastrocnemius muscles. In order to investigate temporal changes on expression of BDNF protein and mRNA after electrical stimulation for 30 min at 1 ms, 40 Hz, BDNF protein was measured at 0, 1, 2, 3 days after stimulation and mRNA was measured at 0, 3, 12, 48 hours. Effects of types of stimulus parameters on the expression of BDNF and mRNA were evaluated by three types of electrical stimulation. Statistical analysis was performed using Mann Whitney-U test and Wilcoxon test.

Results

Expression of BDNF protein after electrical stimulation with 1 ms, 40Hz for 30 min to the sciatic nerve was significantly increased at 1, 2, 3 days after stimulation in the soleus muscle compared to the control (p<0.001) and at 2 and 3 days after stimulation in the medial gastrocnemius muscle (p<0.01) (Fig. 1).
Fig. 1. Time-dependent changes in the expression of BDNF protein in the soleus muscle (SOL) and medial gastrocnemius muscle (MGC) after electrical stimulation to the sciatic nerve with 1 ms, 40 Hz for 30 min. CON represents control animal. *denotes significant difference from control (**p<0.01, ***p<0.001).

Expression of mRNA after electrical stimulation with 1 ms, 40Hz for 30 min was significantly increased at 0, 3, 12, 48 hours after stimulation in the soleus muscle compared to control (p<0.05, 0.01, 0.001, 0.001, respectively) and at 3, 12, 48 hours after stimulation in the medial gastrocnemius muscle (p<0.01, 0.001, 0.001, respectively). Electrical stimulation with 1 ms, 40Hz for 30 min among 3 types of stimulus parameters produced the highest expression of BDNF protein and mRNA in both the soleus and medial gastrocnemius muscles, and the lowest expressions were produced by electrical stimulation with 1 ms, 40Hz for 5 min in both muscles (Fig. 2).

Fig. 2. Effect of stimulus parameters on the expression of BDNF mRNA in the soleus muscle (A) and the medial gastrocnemius muscle (B). CON represents control animal. *denotes significant difference from control (*p<0.05, **p<0.01, ***p<0.001).
Discussion

It is becoming well-established that neurotrophins including BDNF and NT-3 have a role in the development of functional connectivity between skeletal muscle and the spinal cord. BDNF in the spinal cord can stimulate the growth of severed axons and enhance the survival of damaged cells, and can promote functional recovery [3]. BDNF, NT-3 and other neurotrophins produced in skeletal muscle may enhance the potential of innervation of motoneurons and play a critical role in the plasticity of the neuromuscular synapse [4].

Electrical stimulation to the sciatic nerve produced BDNF in the hindlimb muscles in this study, which was more increased than that produced by exercise training [4]. The present results suggest that electrical stimulation may have a greater effect on the production of BDNF in muscles. Gradual increase with time in BDNF mRNA of both muscles was paralleled by a significant increase in BDNF protein. The soleus muscle, mainly composed of slow muscle fibers, produced more BDNF than the medial gastrocnemius muscle by electrical stimulation of the sciatic nerve. This is consistent with chronic electrical stimulation to the sciatic nerve in hindlimb suspended rats preventing muscle atrophy more effectively in the soleus muscle than in the medial gastrocnemius muscle [5]. In parameter of electrical stimulation, the duration of stimulation has a larger potential role on the production of BDNF than does frequency of stimulation. However, the mechanism for BDNF production in the hindlimb muscles by electrical stimulation remains unclear. These findings indicate that electrical stimulation can ameliorate the neuronal plasticity in paralytic muscles by upregulating BDNF mRNA and the types of stimulus parameter may modulate BDNF production.

References


Acknowledgement: This study was supported by a grant of the Korea Health 21 R & D Project, Ministry of Health & Welfare, Republic of Korea (02-PJ1-PG10-21402-0001).