 Decreased Activity in Neuropathic Pain Form and Gene Expression of Cyclin-Dependent Kinase5 and Glycogen Synthase Kinase-3 Beta in Soleus Muscle of Wistar Male Rats

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Background: The relationship between decreased activity/neuropathic pain and gene expression alterations in soleus muscle has remained elusive.

Objectives: In this experimental study, we investigated the effects of decreased activity in neuropathic pain form on Cyclin-Dependent Kinase 5 (CDK5) and Glycogen Synthase Kinase 3-β (GSK-3β) gene expression in soleus muscle of rats.

Materials and Methods: Twelve male Wistar rats were randomly divided into three groups: (1) tight ligation of the L5 spinal nerve (SNL: n = 4); (2) sham surgery (Sham: n = 4), and (3) control (C: n = 4). The threshold to produce a withdrawal response to a mechanical and thermal stimulus was measured using von Frey filaments and radiation heat apparatus, respectively. Following 4 weeks after surgery, the left soleus muscle was removed and mRNA levels were determined by real-time Polymerase Chain Reaction (PCR).

Results: Compared to control animals, L5 ligated animals developed mechanical and heat hypersensitivity during total period of study. Soleus muscle weight as well as CDK5 mRNA levels (less than ~ 0.4 fold) was decreased and GSK-3β mRNA levels (up to ~ 7 folds) increased in L5 ligated animals.

Conclusions: These results showed enhanced muscle atrophy processes following peripheral nerve damage and might provide a useful approach to study underlying muscle mechanisms associated with clinical neuropathic pain syndromes.

Keywords: Neuropathic Pain; Soleus Muscle; CDK5 Protein Kinase

1. Background

Neuropathic pain is a chronic pain defined as a pain caused by damages to or dysfunction of somatosensory system and can expresses itself in the following forms: allodynia, hyperalgesia, and spontaneous pain (1). Along with causing changes to nervous system, neuropathic pain can decrease physical activity levels (2, 3). Furthermore, neuropathic pain can affect structure and function of muscles through muscular atrophy (4, 5). Many studies have proven that models of neuropathic pains will be followed with muscle atrophy (5-8).

However, exact cellular mechanisms, which cause changes after nervous damages are still unknown (8). Cyclin-Dependent Kinases (Cdks) are serine/threonine protein kinases that play key roles in the regulation of cell cycle, initiation of transcription, and control of certain metabolic cascades in mammalian cells (9, 10). Cdks activity has a vital role in different functions of nerve cells such as neuronal growth and migration, cell secretion, dopamine signaling, and cytoskeletal dynamics (10). Glycogen Synthase Kinase-3 (GSK3) is also a serine/threonine kinase that exists in two isoforms of alpha and beta (11) and participate in the modulation of various functions such as cell signaling, growth metabolism, and many other transcriptional regulating survival and death factors in organisms (12). In general, Cdks and GSK-3β are two of the most important protein kinases involved in neuropathic pain signaling (13, 14). Furthermore, the role of these two proteins in the regulation of muscle plasticity has been clearly proved. For example, it has been shown that GSK-3β is necessary in myofibrillar protein loss system and its reduction causes preserving of contractile protein against proteolysis (15). Cdks also has a key role in skeletal muscle’s structure and its function so that it is effective in changing muscle phenotype and essentially these changes come from its effects on cytoskeleton proteins’ structure such as actin and microtubules and regulation of myogenesis (16, 17). On the other hand, changes to expression of Cdks and GSK-3β in muscular and nervous systems after numerous interferences infer such an insight that related systems change through following conditions: chronic state of motor unit activity, afferent activity level toward motor neurons, number of innervated muscle fibers by motor neurons, and metabolic level of target tissue.