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Identification of the effects of peripheral nerves injury on the muscle control – A review

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Impairment of motor function following peripheral nerve injury is a serious clinical problem. Generally nerve injury leads to erroneous control of muscle activity that results in gait and voluntary movement abnormalities followed by muscle atrophy. This article presents a review of studies on the effects of peripheral nerve injury on the motor system performed on animal models. We focused our attention on the results that are fundamental for better understanding of the degenerative and regenerative processes induced by nerve injury as well as of the mechanisms of structural changes in neuronal networks controlling movement. Quoted results are also important for clinical applications because they allow to develop new diagnostic and therapeutic techniques that can be used after nerve injury inducing motor deficits. However, till now no efficient therapy inducing satisfactory recovery was found. There is still a need to continue an advanced basic research directed to develop effective therapies. Thus the aim of this review is to compare the results of recent studies performed on various animal models in order to propose new methods for identification of mechanisms responsible for muscle deficits and propose targets for new pharmacological therapies.

Key words: peripheral nerve, injury, muscle control deficits, locomotion, EMG.

Introduction

Injury to peripheral nervous system (PNS) can often be caused by diseases or by transsection or crush associated with various kinds of accidents (during surgery or bone break). Irrespective of the possible regenerative response of PNF following injury, the functional recovery is often not satisfactory. Injury affects not only the nerves and the neurons but also the muscles and the proprioceptors that are important in control of muscle activity during movement. The severity of symptoms depends on the type of nerves affected (motor, sensory, or autonomic). Common symptoms are gait and voluntary movement abnormalities followed by muscle atrophy as well as changes and even loss in sensation followed by phantom pain. Till now no efficient therapy was found to enhance effective regeneration in central and peripheral nervous system and to induce satisfactory functional recovery.

The effects of degeneration and regeneration following injury on the activity of neuronal networks controlling muscle activity as well as their mechanisms were studied with various experimental methods. In the basic research the animal model of nerve injury is very often used. The mentioned above effects were identified at functional, cellular and molecular levels. To assess functional deficits after PNS injury the locomotor function using animal model is very often investigated. In the majority of studies the deficits of locomotor movements are assessed using behavioral observation only whereas the analysis of electromyographic activity of muscles is used less frequently. The goal of the studies carried out at the cellular level is to quantify the degeneration and regeneration of axons, survival of neurons and proprioceptors. Molecular studies are designed to reveal molecular events associated with the degenerative and regenerative processes and to obtain data for suggesting new potential therapies. Irrespective of the number of studies the knowledge on the mechanisms of the degenerative and regenerative processes following nerve injury as well as their impact on the motor function is still not satisfactory. It shows the need for studies that due to appropriate measurement methods and data analysis could reveal mechanisms of induced injury deficits and to suggest therapies that can limit degeneration and/or augment the regenerative processes.

Most studies on the effects of nerve injury on muscle function were performed on the model of adult rat locomotion. The aim of these studies was to quantify the degree of impairment in early postoperative period and the recovery of motor function after

different types of nerve injury and repair such like direct coaptation and autograft implantation. Studies of injury effects on degenerative and regenerative processes performed at the cellular and molecular level were focused at the identification of molecular processes participating in degeneration and regeneration of nerves, motoneurons and sensory neurons, and proprioceptors. However, less attention was devoted to the alterations induced by injury in the structure and function of the spinal neuronal networks that control the activity of motoneurons.

This article presents a review of studies on the effects of nerve injury on the muscle function. The aim of this review was to analyze and compare the effectiveness of experimental methods used in these studies for development of new strategies that can improve identification of deficits of muscle function and their mechanisms. The most relevant data comes from the experiments on rats with sciatic nerves injured with the method of crush or transsection inflicted at various animal age. Thus this review will be focused mainly on the experiments performed on this model of nerve injury both with the use of behavioral outcome measures and measures of EMG activity of muscles. It will be shown that studies performed with the analysis of EMG activity offer opportunity to reveal specific alteration in muscle control that are hard to deduce.

Effects of nerve injury on the structure of motor control system

Systematic studies of the peripheral nerve injury effects on the motor system were begun in half of last century. Earlier and recent studies documented that degenerative processes following injury involve all the elements of the lowest level of motor control system that is motor and sensory axons, motoneurons as well as sensory neurons and proprioceptors. The effects depend on the animal age at time of injury and its severity. The effect of sciatic nerve crush on the number of surviving motoneurons is now well identified. In last decade of last century it was documented that the vulnerability of motoneurons to injury declines during the first week of postnatal life [10]. In newborn rats it leads to the loss of majority of motor and proprioceptive sensory axons, neurons and synapses as well as affects proprioceptors. This problem was reinvestigated recently and it was shown that after sciatic nerve crush at birth a larger proportion of motoneurons and motor units are lost in the soleus than in extensor digitorum muscle [6]. In adult animals the impairment of neuronal networks elements is less severe due

to partial regeneration and in adulthood almost all motoneurones and axons are able to survive and reinnervate the limb muscles. However, irrespective of the regeneration the recovery of motor function is incomplete. Both in earlier [21] and recent studies [12, 1, 13] lack of complete recovery was attributed not only to the number of regenerating axons and surviving neurons but mainly to the misdirection of regenerating axons. The intensity of the injury effect on the degeneration of proprioceptive sensory axons and death of neurons also depends on the age of animals. However, irrespective of the number of studies before [9, 27, 28, 7, 18, 26] and recently [12] less is known about the impact of sciatic nerve crush on the action of proprioceptive feedback because it also induces degeneration of proprioceptors.

Methods of motor deficits measurement and data analysis

The effects of nerve injury on the muscle control and function recovery were most frequently investigated on the model of rat locomotion using the method of sciatic nerve crush. However, the analysis of EMG activity was rarely used to assess the deficits of locomotor movement. On the other hand the behavioral outcome measures were used in the majority of studies [for review see 24]. In some studies [15, 22] the postoperative changes in gait were quantified using only the 21 point Basso-Beattie-Bresnahan (BBB) scale [3] or the number of slips during the locomotor movement on beam [19]. Among the direct indices of movement, the joint angles were used to quantify the postoperative changes in the kinematics of ankle during unrestrained locomotion in rats [13, 2]. Both, in the earlier and recent studies, gait was assessed using locomotor speed, step cycle and stance phase durations measured directly with the use of camera or recently with the use of CatWalk system that allowed also the analysis of limb coupling and pattern of limb recruitment [24, 4, 5]. However, in the majority of these studies, deficits in locomotor movements were described using the mean values of analyzed indices, whereas relationships between them were not used to better characterize animal performance.

The analysis of EMG muscle activity during unrestrained locomotion was used more frequently in the previous studies [e.g. 11, 16, 17, 20, 8]. However, the quantitative analysis was limited to the homologous muscle pairs, whereas the characteristics of the antagonistic muscle activities including their recruitment and

coordination were assessed qualitatively only as was showed in given above publications and the recent one [14].

Discussion

Irrespective of the number of studies their results are difficult to generalize and the comparison of results is hampered by the differences in the experimental animals, animal age at the time of injury, the injured nerves and the methods of injury as well as the methods of measurement and data analysis. Generally, the methods using behavioural measures did not offer the sensitivity that is necessary to detect specific postoperative alterations in muscle control. The deficits in the muscle activities and the effects of recovery could hardly be recognized due to that the effects of malfunction of muscles with their nerve injured on limb performance might be masked by the performance of synergic muscles. In some studies the effects of injury and recovery were characterized using mean values of the analyzed indices only and the complete recovery of function was suggested when means corresponding to the nerve injured and intact limbs were similar.

The quantitative analysis of EMG activity during locomotion was limited to the analysis of step cycle and muscle activity duration as well as the relationship between these variables. The coordination and recruitment of homologous and antagonistic muscle activities were not studied quantitatively. In addition, the duty factors of muscle activities and the relationship between the duty factor and the step cycle duration as well as the relationship between duty factors of intact and nerve injured side muscle activities were not analyzed in spite that such analysis is crucial to asses muscle control in respect with the prerequisites of normal locomotion. It is important to note that analysis of muscle EMG activity allows to propose more sensitive measures for describing an injury induced impairment of muscle control than the behavioral ones. The main symptom of impairment were changes in the activity duration as well as in the relationship between the durations of muscle activity and step cycle [16, 17, 20, 8, 14]. Generally in rats with sciatic nerve crushed the activity of extensor muscles was shorter whereas the activity of flexors was distinctly longer compared to those of non-injured side muscles. The effect of injury on the parameters of the relationship between the extensor muscle activity duration and the step cycle duration manifested

by low value of the correlation coefficient, flat slope and the intercept increased towards zero whereas the relationship corresponding to intact muscle was strong with negative intercept. Unfortunately the parameters of relationship for duty factor of muscle activity, which is the duration of muscle activity expressed in the percent of step cycle duration, were not used to assess muscle control impairment and infer about the respective mechanism. In normal locomotion, not only activity duration but also duty factor is well correlated with the step cycle duration and the slopes of respective relationships are positive. In addition, in normal locomotion duty factors of homologous muscles are also well correlated and correlation coefficient is a sensitive measure of the muscle coordination. Thus data analysis limited to the mean values of indices and the parameters of the relationship between the muscle activity duration and the step cycle duration could not reveal muscle control impairment if it was characterized by the lack of correlation between the duty factor and the step cycle duration. In addition methods of data analysis used in previous studies could not assess the coordination between nerve injured and intact muscle activities in terms of duty factors correlation, which should be strong if the recovery of muscle activity control is to be assessed as good.

A severe deficit of muscle control observed in a few studies before [17, 20, 8] and recently [14, 6] was an excessively long activity of flexor muscles resulting in the coactivation with the activity of extensors. Such activity of antagonistic muscles is not observed in normal locomotion. However, in none of the studies it was analyzed quantitatively to reveal the mechanism of this postoperative change. In normal locomotion antagonistic muscles demonstrate coordination of activity almost “out of phase” that limits coactivation of both muscles to very short time interval during the step cycle. In contrast, the coactivation of antagonistic muscles after nerve injury may suggest that networks controlling antagonistic muscles can be coordinated “in phase”. It is worth to note that recently Sabatier et al. [14] demonstrated that the coactivation of antagonistic muscles in rats with sciatic nerve injury could not be attributed only to the misdirection of regenerating axons. All these data suggest that nerve injury produced also a change in the interaction between the neuronal networks controlling individual muscles that resulted in erroneous coordination of the neuronal networks and muscle activities. Thus, studies on the mechanisms of muscle coordination designed with specific methods of data analysis are necessary to reveal the neuronal mechanism of this malfunction and potential target for pharmacological therapy.

Summary

In summary, both previous and recent studies showed that the injury of peripheral nerves induces processes that affect muscle fibres, motor and sensory axons and neurons and suggested that injury can affect also the coordination of neuronal networks at the lowest level of motor control system. Irrespective of the number of experimental studies the mechanisms of nerve injury effects are still not recognized sufficiently to design neuroprotective and/or restorative therapies. It shows that further experimental studies on the mechanisms of peripheral nerve injury effects are required.

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