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Features of bioelectrical activity of interneurons pools of the spinal cord on early experimental compression neuropathy and testosterone effects

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Abstract
Background: special attention has been paid to compression neuropathy disclosure mechanisms in the early stages of its development and impact on the process of biologically active substances such as hormones. The ability of sex hormones affect the rate of protein metabolism and, consequently and causes changes in the electrical activity of neurons in the central nervous system caused so that it is necessary to study the impact of testosterone of on the development of post denervation hyperreflexia.
Methods: the aim of present study was to explore features of bioelectrical activity of interneurons pools of the spinal cord on early experimental compression neuropathy and testosterone effects.
Results: in conditions of experimental compression neuropathy against the background of testosterone introduction observed changes in the activity of neurons posterior horns of spinal cord, shown to reduce the occurrence threshold of potential of dorsal surface of spinal cord. Changes of chronaxie of dorsal surface potential significant about changes of biophysical characteristics of Na^+-channels, and require more detailed study.
Conclusions: metabolic transformation in conditions of compression neuropathy against the background of the introduction of testosterone leads to decrease threshold and fails to operate afferent conductors interneurons pools of spinal cord.

Keywords: spinal cord, dorsal surface potential, compression neuropathy

Introduction
Multiple data of neurological and neurosurgical studies have concluded significant increase in the prevalence of lesions of central and peripheral nervous system [8, 15]. One of the leading place is taken by the compression neuropathy [2, 15]. Despite the large number of observations on this issue, the problem of the consequences of clinical guidelines currently does not lose its relevance [2, 7, 8]. One of the main clinical manifestations of compression neuropathy is neuropathic pain, which manifests itself in the form of hyperesthesia, and paresthesia, synesthesia that significantly affects the quality of patients life [4, 6, 8, 9, 12]. The primary role in the development of these manifestations belongs the damage of peripheral sensory fibers and neurochemical changes in the metabolism of spinal neurons [5, 6].
The primary role in the development of these manifestations belongs the damage of peripheral sensory fibers and neurochemical changes in the metabolism of neurons posterior horns of the spinal cord.
Already been experimentally proved that in the early stages of onset (1 to 2 weeks) amplified speed of change and amplitude of action potentials of different types of fibers that make up the dorsal root of spinal cord [10]. Conflicting data regarding changes of electrophysiological parameters of spinal cord in studies with different disease duration on clinical guidelines motivated us to a more detailed analysis of the dynamics of excitation occurring in spinal cord experimental animals with clinical guidelines in the early period (1 - 10 day of the experiment start). In previous studies of our laboratory under conditions of prolonged denervation of the lower limbs were found significant changes in segmental structures in the spinal cord [10, 11].
Special attention has been paid to compression neuropathy disclosure mechanisms in the early stages of its development and impact on the process of biologically active substances such as hormones. The ability of sex hormones affect the rate of protein metabolism and, consequently cause changes in the electrical activity of neurons in the central nervous system caused so that it is necessary to study the impact of testosterone of on the development of post denervation hyperreflexia [3].
In our studies, we used the method of recording potencial of dorsal surface of spinal cord as

integral indicators characterizing the activity of interneurons of spinal cord, which occurs in response to afferent fibers stimulation.

Materials and methods

Experimental Animals

Research carried out on 40 mature rats aged 6-8 months weighing 180-250 g, Wistar line. They were housed in regular cages at constant temperature (22±2 ºC) with 12 h light/dark cycle and standard water-food diet.

Experiments were conducted according to European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose (Strasbourg, 1986); Directive 2010/63/EU on the protection of animals used for scientific purposes, and were approved by the Institutional Animal Care Committee.

Study design

The animals were divided into two groups:

a) "intact animals» (n = 10)
b) "animals with simulated state» (n = 30).

Compression neuropathy was modeled by ligation of the sciatic nerve at the level of the upper third of the thigh by silk ligature under ether anesthesia. The animals of the group "model group" daily injected solution of Testosterone propionate (Pharmaceutical Company «Zdorovie» Ltd at a dose of 1 mg / kg. In acute experiment on animals was carried on 1,3,5,7 and 10 the day after simulation of compression neuropathy. During tiopentalium anesthesia (50 mg/kg) was performed laminectomy with dissection of the dura mater of spinal cord. After this was completed section of the spinal cord at the level of Th12-L1. After hordotomy, spinal cord was poured by the layer of Vaseline oil. The animals was held for three hours in the 36-37 ºC temperature range [10, 11].

Electrophysiological studies

In acute experiments on the central part of the spinal root (L5), impose the irritant bipolar electrodes, was carried stimulation by rectangular pulses with a duration of 0,3 ms and strength from 1 to 5 thresholds. We used the methodology of twice stimulations on the back spinal root (L5) at intervals of 2 to 1000 ms. For diverted the dorsal surface potential of spinal cord we used monopolar ball silver electrode. The extraction was carried out from the spinal cord in focus of maximum activity, reference electrode thus placed on the muscles of the lower extremity [9, 10, 13]. For stimulation we used standard electrophysiological equipment. Recording bioelectric responses was performed by analog-to-digital converter and PC.

We investigated the following parameters of dorsal surface potential of the spinal cord: the threshold, chronaxy, durations of the: latent period, afferents peak, N_1, N_2, N_3 components and P-waves, investigated a total duration of potential and amplitudes of: afferents peak, N_1, N_2, N_3 components and P-waves [14]

Statistical Analysis

For processing of results was used the methods of variation statistics: calculation of visibility percentage, arithmetic mean number (M) and the average error (m). Evaluation of reliability conducted by methods of nonparametric statistics (Mann-Whitney criterion). Changes considered reliable indicators at $p<0,05$ [13].

Results

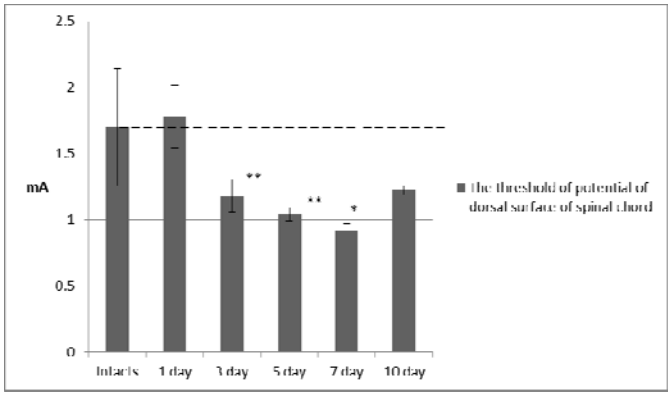
The results of study of dorsal surface of the spinal cord in intact group of animals we have established: occurrence threshold was 1,7 (± 0,44) mA. Chronaxye was 87 (± 19,52) microseconds. The latent period was 0,25 (± 0,04) ms. Duration dorsal surface potential in intact animals was 16,60 (± 0,97) ms.

Average amplitude characteristics of potential of dorsal surface of spinal cord ater the supramaximal stimulation of dorsal root in intact animals obtained in this study are presented in Table 1.

Table 1: Averages amplitudes of components of potential of dorsal surface of the spinal cord in intact animals (n = 10)

Indicator	Afferents peak amplitude (mV)	N_1-component amplitude (mV)	N_2-component amplitude (mV)	N_3-component amplitude (mV)	P-wave amplitude (mV)
M±m	2,15 (±0,07)	2,8 (±0,086)	1,98 (±0,12)	0,41 (±0,09)	0,34 (±0,056)

Compared with the intact group of rats in the experimental group with the experimental compressive neuropathy in the background the introduction of testosterone we received progressive lowering of the threshold of potential of dorsal surface with a minimum on the seventh day of the experiment, which was 0,92 (± 0,05) mA (n = 6; p <0.01) (Fig. 1)

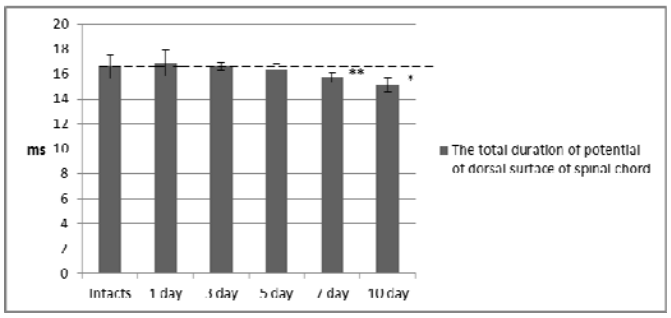


* - statistically significant difference $p<0.01$;
** - statistically significant difference $p<0.05$.
----- - the level of the intact group

Fig 1: The threshold of occurrence of the potential of dorsal surface of the spinal cord in intact group and in different terms after ligation of the sciatic nerve on the background of the introduction of testosterone (1 mg/kg).

The shortening of chronaxy with the minimum on the seventh day after ligation of the sciatic nerve on the background of the introduction of testosterone, was founded. The duration of the latent period in the experimental group of animals with compressive neuropathy was reduced. It was minimal on the fifth day of the experiment and was 0,18 ± 0,024 ms (n = 6, p <0.01)

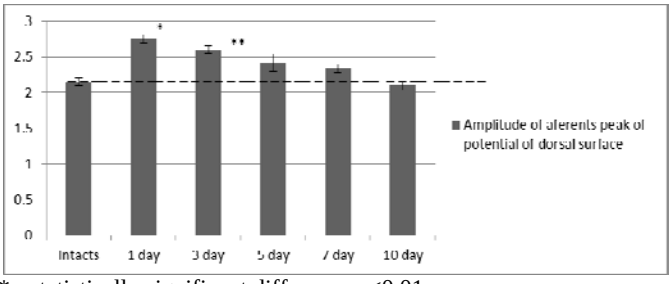
Duration of dorsal surface potential of the spinal cord in the intact group was 16,60 ± 0,0,97, and in the "model" group it progressively decreased. It has minimal value on with 10-th day – 15,12 ± 0,56 (ms.). (Fig. 2)



* - statistically significant difference p<0.01;
** - statistically significant difference p<0.05.
----- - the level of the intact group

Fig 2: The total duration of potential of dorsal surface of the spinal cord in intact group and in different terms after ligation of the sciatic nerve on the background of the introduction of testosterone (1 mg/kg).

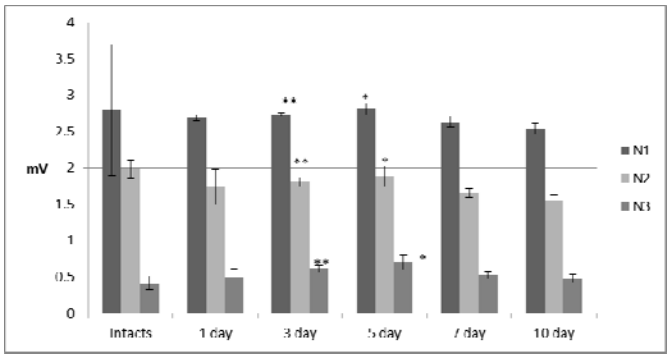
Consider the changes in the amplitude of components of potential of dorsal surface of the spinal cord (Fig. 3). It has been found the afferents peak amplitude increase compared to the intact group on the first day after ligation of the sciatic nerve at 27,9% (2,75 ± 0,06 mV; n = 6, p <0.01). However, the third day of decline there, and on the tenth day it was 2,10 ± 0,06 mV (n = 6).



* - statistically significant difference p<0.01;
** - statistically significant difference p<0.05.
----- - the level of the intact group

Fig 3: Afferents peak amplitude of the potential of the dorsal surface of the spinal cord intact group and in different terms after ligation of the sciatic nerve on the background of the introduction of testosterone (1 mg/kg).

Quite interesting were changes in the amplitude N_1, N_2 and N_3 components of dorsal surface potential of the spinal cord. Compared with the intact group we observed an increase of the amplitude N_1, N_2 and N_3 components to 5-th days of our study (Fig. 4).



* - statistically significant difference p<0.01;
** - statistically significant difference p<0.05.

Fig 4: The amplitude of N_1, N_2 and N_3 components of potential of dorsal surface of the spinal cord in intact group and in different terms after ligation of the sciatic nerve on the background of the introduction of testosterone (1 mg/kg).

A significant change in the amplitude of P-wave of potential of the dorsal surface wasn't found (p> 0.01).

We studied changes of dorsal surface potential of the spinal cord in response to a pair stimulation of spinal dorsal root. It was revealed an interesting pattern that processes segmental inhibition of afferent components, N_1-component progressive reduced to the tenth day of the experiment (Fig. 5).

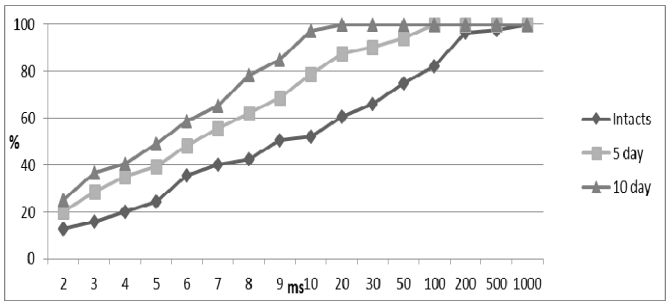


Fig 5: Dynamics of recovery in amplitude of N_1- component in response to pair stimulation of the dorsal root of spinal cord.

Discussion

Some authors point to a significant role Na^+-channels of neurons of posterior horns of the spinal cord. The expression of Na^+-channels in conditions of compression neuropathy and input current were increased and caused of reduces the excitability threshold [1, 4, 5, 10].

In our study, this process can be enhanced by anabolic effects of testosterone [3].

Proved that testosterone increases protein synthesis in cells, has a pronounced anabolic effect. Thus increasing the number of integral membrane proteins, which are ionic channels. Restructuring of neuronal membranes leads to excessive entry to the cell ions Na^+ and Ca^{2+}. In our opinion this process is the biochemical substrate of the phenomenon of increased excitability [10, 13, 16]. In turn phenomenon of increased excitability can cause stronger afferentiation flow that contributes to neuropathic pain and hyperesthesia in conditions of compression neuropathy.

Chronaxy changes indirectly characterizes the activity of Na^+-channels. Discovered in our studies changes about reducing of chronaxy of dorsal surface potential coincides with the findings of other authors [10, 3]. However, in this case, increased expression of Na^{2+}-channels may be due to the direct influence of testosterone on protein synthesis.

In the analysis of dorsal surface potential of the spinal cord, we have used force supramaxymal irritation (5 thresholds), which is enough to activate all low-threshold aferents [10, 11, 13, 14]. In conditions of known strength of stimulation we observed the maximal saturation of dorsal surface potential. The following increase of the irritation of intensity did not cause growth of amplitude.

We founded that under the experimental compression neuropathy was significant (p<0,05) increase of only N-components amplitude that show polysynaptic activity of nonsegmental interneurons [11, 10, 13].

As you know, the afferent peak is the total initial wave of excitation of low-threshold afferents [10, 13]. Installed, the increase of amplitude of afferent peak on the background of the introduction of testosterone indicated afferentiation entrance to the spinal cord.

Significant reduction of N_1-component inhibition may indicate that administration of testosterone in conditions of compressive neuropathy aimed at reducing of presynaptic inhibition.

Conclusions

In conditions of experimental compression neuropathy against the background of the introduction of testosterone was found changes in the activity of neurons posterior horns of the spinal cord that is manifested in the reduction of the threshold potential occurrence dorsal surface of the spinal cord. Changes of chronaxy indicated about significant changes of biophysical characteristics Na^{2+}-channels, and require more detailed study.

The metabolic transformation in conditions of compression neuropathy against the background of the introduction of testosterone leads to threshold decrease and violations in functioning of afferent and interneurons pools of spinal cord.

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