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The Influence of Gliatilin on Excitability of Spinal Motorneurons After Spinal Cord Contusion

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Abstract
In this study we evaluated the influence of gliatilin on the level of excitability of spinal motorneurons and on the functional state of peripheral part of the neuromotor system after spinal cord contusion. Two periods of a traumatic illness were evaluated with electromyography on dog's model. Compare with control animals, in group that received gliatilin we observed a stable level of excitability of spinal motorneurons and functioning of peripheral part of the neuromotor system. It is suggested that gliatilin, being a donor of a glitcerophosphat, could maintain the integrity of neural cells membranes by restoration of the synthesis of phospholipids and carries out a neuroprotective effect.

1. Introduction

Every year about 22 million people worldwide have SCI and almost all of them later have long-term disability (Zhou, et al., 2014). Several methodological approaches were suggested to regain motor functions after spinal cord injury by using spinal cord stimulation (Gerasimenko et al., 2001; Nandra et al., 2011; Lavrov et al., 2015), pharmacological activation of the spinal networks (Lavrov and Cheng, 2004; Gerasimenko et al., 2009), bypassing the injury site (Gad et al., 2013). However, the correction of the secondary changes caused by a spinal trauma appears to be the one of the most important problem in this direction (Hall, Springer, 2004; Hall, 2011; Wang, et al., 2015). Many of the current studies particularly focus on acute period of trauma with attempt to apply neuroprotective agents as soon as possible to prevent the secondary damage and preserve neural cells (Kwon et al., 2011). Gliatilin (choline alphoscerate), semi-synthetic derivative of lecithin, is a precurssor of the endogenous choline and has the ability to incorparate in the brain phospholipids during the first 24 h after injection. This leads to the fast increase of the free choline level in plasma that distinguishes gliatilin from the other precurssors of choline (Abbiati et al., 1993). Preclinical research shows that gliatilin can increase the release of acetylcholine in rats' hipocamp and facilitate their training and memory (Amenta et al., 1993). Its increases the synthesis and release of acetylcholine, improves the efficiency of synaptic transport (Tomassoni et al., 2012), considerably reduces glial reactions in a rats hipocamp SHspR (Tomassoni et al., 2006). All these data suggest that gliatilin has neuroprotective effect on brain tissue. An ability of phospholipids to maintain the integrity of neural cells membranes by restoration of the synthesis of phospholipids and acetylcholine became the basis for the assumption that gliatelin can be used as a neuroprotective agent for SCI. In this study we have investigated

the influence of a gliatilin on the level of excitability of spinal motoneurons and functioning of the peripheral part of the neuromotor system at the different periods after an experimental contusion of spinal cord in dogs.

2. Materials and Methods

All experiments were performed on 12 dogs, both genders, weight 15±5 kg, 1 year of age. All animals were handled in identical conditions of a vivarium. Surgical procedures were performed in sterile operation room under ketamine, which has a long effect and doesn't show negative impacts on the blood circulatory systems and respiration. Gliatilin was injected intramuscularly in a dose of 5,5 mg/kg.

2.1. Experimental SCI Procedure

Spinal cord contusion was performed at the first lumbar vertebra (L1). After laminektomiya of L1 (the dura mater remained intact) a spinal cord injury was performed according to the modified technique of A. Allenae (1911), by placing a metal pipe 20 cm high on a vertebra and dropping on it a weight of 20 g (Anderson et al., 1985). Muscular contraction in the lower extremities was used as a control of damage as well as visualization of the bruise on the spinal cord. The falling weight and a tube **were** removed after injury. All experiments were performed according to the bioethical standards. Animal care was carried out according to requirements No. 742 from 13. 11. 1984. "Rule of work with use of experimental animals" which act to the present and the Directive of the European parliament and Council of September 22, 2010 for protection of the animals used for the scientific purposes (Directive 2010/63/UE on the protection of animals used for scientific purposes).

After an experimental contusion all animals were divided into the experimental groups. In the first group all animals received no therapy in the post-traumatic period. In the second group, one day after injury animals received intramuscular injections of gliatilin at 100 mg/kg, 1 time per day within 10 days.

2.2. EMG Recordings

In both groups electromyography was performed before the surgery (intact animals), at 1-3 days, and at 4-21 days after traumatic injury. Needle electrodes were used to register H- and M-responses of a square muscle of a sole to electric stimulation of a tibial nerve on both right and left sides. The stimulating needle electrodes were entered into the area of projection of tibial nerve on the right and left sides, intensity of stimulation was varied from 0,35 V to 60 V with duration of 0,5 ms. The following parameters of H- and M-responses were analyzed: the latent period (LP) – time from the beginning of stimulus to the first deviation of a wave; amplitude of the maximum responses (A max) – the distance from the maximum positive peak to the maximum negative peak; the size of the ratio of the maximum amplitudes of H- and M-responses (Hmax/Mmax), in % (Iafarova et al., 2014).

2.3. Statistical Analyses

The results were processed with a package of the Biostat programs. All data are reported as mean ± SEM. Statistically significant differences were determined with use of Wilconson test.

3. Results

In the first group of animals right after contusion we observed an increase in LP of M-responses, in both tested periods (Figure 1, gray columns). Thus, LP by 21 days after SCI was increased by 17% ($p<0.05$) in the 1 group. In the second group with gliatilin LP of the M-response was increased, but didn't changed compare to control. In the early period after SCI LP of the M-response decreased by 10% ($p<0.05$) (Figure 1, the shaded columns).

In the first group of animals (without gliatilin therapy) the progressive decrease of the maximum amplitude of M-responses was observed (Figure 2).

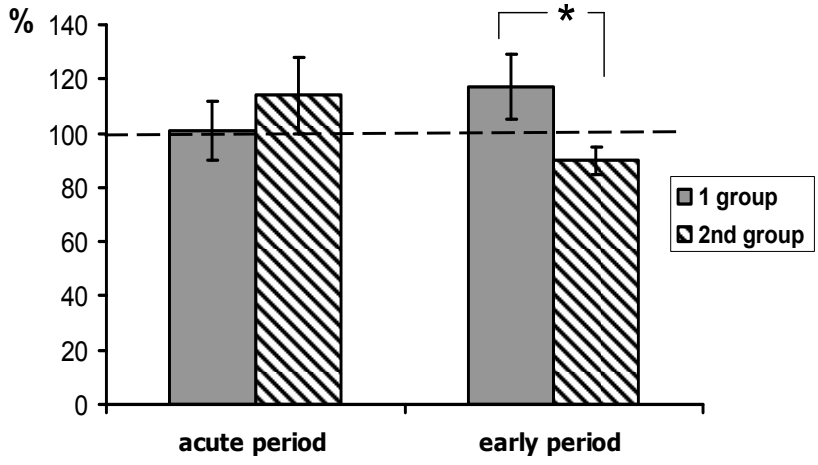

Figure 1. *Change of the latent period of M-responses of a square muscle after spinal cord contusion. On X axis - time after injury: acute period (up to 3 days) and early period (up to 21 days). On Y axis - values of the latent period (LP) of the M-response in % compare to the values before contusion; 1 group (gray columns) animals with an injury with no therapy, the 2nd group - animals with gliatilin therapy. Significant difference between at P < 0.05.*

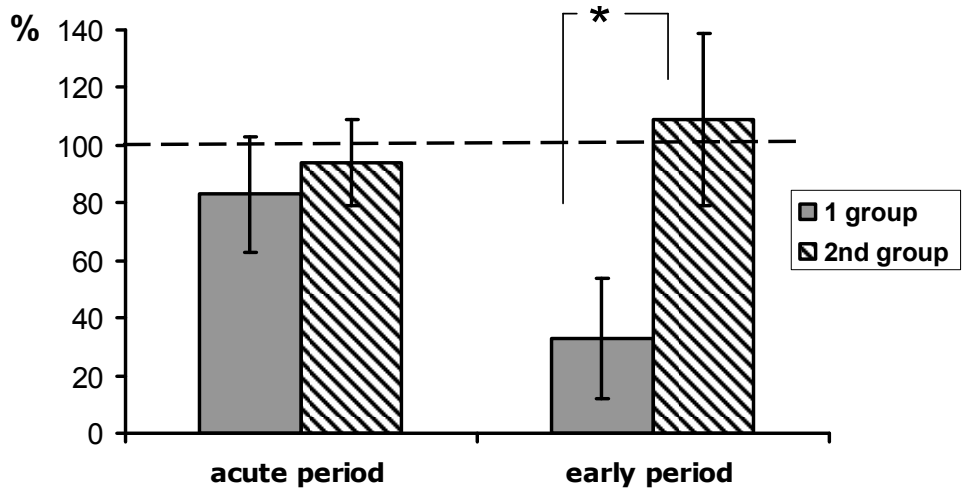

Figure 2. *Change of the amplitude of M-responses of a square muscle after spinal cord contusion. Abbreviations, same as in Fig. 1.*

As it presented on Figure 2, the maximum amplitude of M-response in acute period was decreased by 20% from presurgical level. In the early period after injury it decreased almost by 3 times. In the second group of animals with gliatilin therapy (Figure 2, shaded columns), the maximum amplitude of M-response of a square muscle of a sole didn't changed from presurgical level throughout experiment, however, in comparison with group 1, it was higher, and by 21 days amplitude averaged was 109±30%. In the first group of animals Hmax/Mmax ratio in the acute period was 130±24% of a reference level, and in the early period raised up to 180±25% ($p<0,05$) (Figure 3, gray columns).

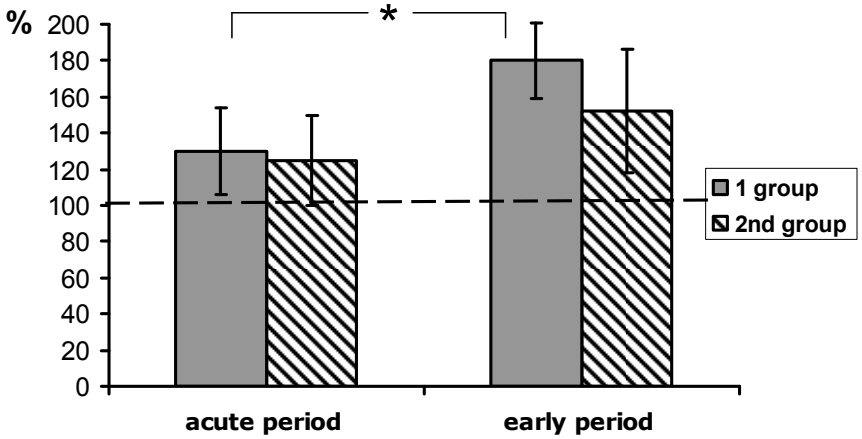

Figure 3. *Change of the ratio of the amplitudes of H- and M- responses (H max/ M max) after spinal cord contusion. Abbreviations, same as in Fig. 1.*

In the second group of animals the ratio Hmax/Mmax was not significantly different compare to the control level (Figure 3, the shaded columns).

4. Conclusion

According to present results, gliatilin can promote stabilization of the level of reflex excitability of spinal motorneurons after SCI. It is possible to assume that gliatilin being a donor of a glycerophosphate, maintains integrity of membranes of neural cells by restoration of synthesis of phospholipids and carries out a neuroprotective effect saving spinal motorneurons. These results can testify to efficiency of application of gliatilin in the early period of a traumatic SCI.

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