

EFFECT OF ACUTE LATERAL HEMISECTION OF THE SPINAL CORD ON SPINAL NEURONS OF POSTURAL NETWORKS

P. V. ZELENIN, V. F. LYALKA, G. N. ORLOVSKY AND T. G. DELIAGINA *

Department of Neuroscience, Karolinska Institute, SE-17177 Stockholm, Sweden

Abstract—In quadrupeds, acute lateral hemisection of the spinal cord (LHS) severely impairs postural functions, which recover over time. Postural limb reflexes (PLRs) represent a substantial component of postural corrections in intact animals. The aim of the present study was to characterize the effects of acute LHS on two populations of spinal neurons (F and E) mediating PLRs. For this purpose, in decerebrate rabbits, responses of individual neurons from L5 to stimulation causing PLRs were recorded before and during reversible LHS (caused by temporal cold block of signal transmission in lateral spinal pathways at L1), as well as after acute surgical LHS at L1. Results obtained after Sur-LHS were compared to control data obtained in our previous study. We found that acute LHS caused disappearance of PLRs on the affected side. It also changed a proportion of different types of neurons on that side. A significant decrease and increase in the proportion of F- and non-modulated neurons, respectively, was found. LHS caused a significant decrease in most parameters of activity in F-neurons located in the ventral horn on the lesioned side and in E-neurons of the dorsal horn on both sides. These changes were caused by a significant decrease in the efficacy of posture-related sensory input from the ipsilateral limb to F-neurons, and from the contralateral limb to both F- and E-neurons. These distortions in operation of postural networks underlie the impairment of postural control after acute LHS, and represent a starting point for the subsequent recovery of postural functions. © 2016 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: spinal cord injury, spinal neurons, postural reflexes, cat, spinal networks.

INTRODUCTION

In quadrupeds, a major motor deficit caused by the lateral hemisection of the spinal cord (LHS) at the low thoracic level is paralysis of the ipsilateral hindlimb,

while the contralateral hindlimb suffers much less. A dramatic left-right asymmetry in the muscular tone and limb reflexes prevents normal operation of spinal and supraspinal mechanisms responsible for standing and walking in the hindquarters. However, these functions mostly recover in a few weeks post-lesion (Hultborn and Malmsten, 1983; Helgren and Goldberger, 1993; Kutz-Buschbeck et al., 1996; Frigon and Rossignol, 2006). Our studies on rabbits balancing on a tilting platform have shown that LHS at T12 caused a loss of balance in the hindquarters, but close-to-normal postural reactions to tilts recovered in 2–3 weeks after LHS (Lyalka et al., 2005).

In terrestrial quadrupeds, the dorsal-side-up trunk orientation is maintained due to the activity of the postural system driven mainly by somatosensory information from limb mechanoreceptors (Inglis and Macpherson, 1995; Deliagina et al., 2000, 2006, 2012; Beloozerova et al., 2003; Stapley and Drew, 2009; Horak and Macpherson, 1996). It was shown that organization of the system responsible for stabilization of the trunk orientation in the transverse plane is similar in the cat and rabbit. In both animals the nervous mechanisms controlling orientation of the anterior and posterior parts of the body can operate independently of each other (Beloozerova et al., 2003; Deliagina et al., 2006).

Earlier, in decerebrate rabbits, we studied postural limb reflexes (PLRs). It was suggested that PLRs in intact animals substantially contribute to postural corrections generated during standing (Musienko et al., 2008, 2010; Deliagina et al., 2012). Recently, in decerebrate cat, we demonstrated that PLRs contribute also to maintenance of lateral stability of the hindquarters during locomotion (Musienko et al., 2014). We have shown that PLRs are generated mainly in response to somatosensory inputs from the ipsilateral limb (Musienko et al., 2010). It was also found that the spinal cord contains neuronal networks generating spinal PLRs. However, their efficacy is low, and supraspinal influences substantially contribute to generation of PLRs (Musienko et al., 2010; Deliagina et al., 2014). Recently, two populations of spinal neurons (F and E) contributing to generation of PLRs have been characterized (Hsu et al., 2012; Zelenin et al., 2015). During PLRs, F-neurons were excited in phase with extensors of the ipsilateral limb, while E-neurons – in antiphase.

The overall goal of our current research is to reveal the changes in postural networks underlying the recovery of postural functions after LHS. The aim of the

*Corresponding author. Fax: +46 8 349 544.

E-mail address: Tatiana.Deliagina@ki.se (T. G. Deliagina).

Abbreviations: Co-, contralateral; EMG, electromyogram; Ipsi-, ipsilateral; LHS, lateral hemisection of the spinal cord; PLRs, postural limb reflexes; Rev-LHS, reversible lateral hemisection of the spinal cord; Sur-LHS, surgical lateral hemisection of the spinal cord.

present study was to characterize in detail the starting point for these changes that is the state of the postural networks at the acute stage of LHS. For this purpose, decerebrate rabbits were used. First, in experiments with reversible (Rev) LHS (that is a temporal cold block of signal transmission in spinal pathways on one side), which allowed recording the same spinal neurons before and during their deprivation of unilateral supraspinal drive, we demonstrated that it did not change the phase of the response to stimulation causing PLRs in majority of F- and E-neurons. Thus, F- and E-neurons recorded after acute surgical (Sur) LHS are neurons of spinal postural networks. Second, to characterize in detail the changes in activity of spinal neurons of postural networks caused by LHS, their activity in L5 was recorded in rabbits with Sur-LHS at T12 during somatosensory stimulation causing PLRs in intact subjects. The results were compared with control data obtained in our previous study (Zelenin et al., 2015).

We found drastic right-left asymmetry in PLRs after LHS, which explains the lateral instability observed after the injury. We have delineated the gray matter areas, in which LHS caused reduction in activity of PLR-related neurons, and demonstrated specific changes in the efficacy of posture-related sensory inputs to them.

A brief account of this study was published in abstract form (Deliagina et al., 2013).

METHODS

Two types of experiments (with Rev-LHS, $N = 12$, and with Sur-LHS, $N = 7$) were carried out on adult New Zealand rabbits (weighing 2.5–3.0 kg). All experiments were conducted in accordance with NIH guidelines and were approved by the local ethics committee (Norra Djurförsöksetiska Nämnden) in Stockholm. The main methods were similar to those used in our previous studies (Zelenin et al., 2013, 2015). They are briefly described below. The data obtained in experiments with Sur-LHS are compared with the control data taken from the database of our previous study. The experimental subjects, as well as all methods used in the present study in experiments with Sur-LHS were similar (except for Sur-LHS) to those used in the control study (Zelenin et al., 2015). The control data for F-, E- and non-modulated neurons were published earlier (Zelenin et al., 2015 and Zelenin et al., 2016, respectively).

Surgical procedures

The animal was injected with propofol (average dose, 10 mg/kg, administrated intravenously) for induction of anesthesia, which was continued on isoflurane (1.5–2.5%) delivered in O₂. The trachea was cannulated. The spinal cord was exposed by laminectomy at T12–L2 (for the subsequent Sur-LHS or for placing of the cooling element), as well as at L5 (for recording of neurons). In experiments with Sur-LHS, at L1, the dura mater was removed for subsequent spinal cord lesion. Small holes (~1 mm²) were made in the dura mater at L5 to insert the recording microelectrode. Bipolar electromyogram (EMG) electrodes were inserted bilaterally into two

representative extensors: gastrocnemius lateralis (ankle extensor) and vastus lateralis (knee extensor).

The animal was then decerebrated at the precollicular-postmammillary level (Musienko et al., 2008). After decerebration, the anesthesia was discontinued. In 1 h after cessation of anesthesia, to examine the functional state of the preparation, PLRs were tested (see below). Only preparations with rather stable extensor tonus and pronounced PLRs, which are important attributes of postural activity (Musienko et al., 2008, 2010) were used for experiments. Then, in experiments with Sur-LHS, left or right half of the spinal cord was transected using micro scissors. During the experiment, the rectal temperature and mean blood pressure of the animal were continuously monitored and were kept at 37–38 °C and at greater than 90 mmHg, respectively. Recordings of neurons began 30–40 min after hemisection.

Experimental design

The head and vertebral column of the decerebrate rabbit were rigidly fixed; the forelimbs were suspended in a hammock (Fig. 1A). The method of induction of PLRs was similar to that described earlier (Musienko et al., 2010; Hsu et al., 2012). In short, the hindlimbs of the rabbit were positioned on the horizontal platform, with limb configuration and the inter-feet distance similar to that observed in freely standing rabbits (Beloozerova et al., 2003). The platform as a whole, or its right or left parts separately, could be tilted periodically by rotation around the medial axis with the amplitude $\pm 20^\circ$ (Fig. 1C–E). Since the vertebrate column and pelvis were fixed, tilts of the whole platform led to flexion/extension movements of the hip, knee and ankle joints and close-to-vertical displacements of the distal point of the limb. A time trajectory of tilting the platform and, therefore, a time trajectory of the foot displacement was trapezoidal with a period of ~6 s (Fig. 2A, B), transition between extreme positions lasted for ~0.5 s, and each extreme position was maintained for ~2.5 s. The tilt angle of each platform was monitored with a mechanical sensor. The contact forces under the limbs were measured by means of force sensors (Force in Fig. 1C). In subjects with intact spinal cord, the tilt-related somatosensory stimulation (caused by loading and flexion of the limb on the platform side moving up, and unloading and extension of the limb on the platform side moving down) evoked PLRs (Figs. 2A, 3A, before cooling), which included activation of extensors in the flexing limb and an increase in its contact force, as well as inactivation of extensors in the extending limb and a decrease in its contact force (Musienko et al., 2010).

Reversible LHS

Experiments with Rev-LHS were based on the technique of blocking the spike propagation in spinal pathways by means of cooling; this technique was adapted from our previous study, where it was described in detail (Deliagina et al., 1983; Zelenin et al., 2013). In short, for better thermo-conductance, the cooler was made of a silver plate, and its shape replicated the shape of the spinal cord. A cooling agent was pumped through a tube soldered

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