THE MECHANISMS OF CENTRAL PATTERN GENERATOR ACTIVATION BY MEANS OF EPIDURAL SPINAL CORD STIMULATION

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Abstract –*In paraplegic patients the epidural spinal cord stimulation applied to the dorsal surface of the second lumbar segment produced locomotor-like EMG activity of of the legs muscles. The initiation of stepping can be provoked by the SCS with the definite parameters of stimulation. It was found that the locomotor-like activity arising under SCS is connected with the amplitude modulation of monosynaptic reflexes in extensor muscles and with the switching of monosynaptic to polysynaptic pathways activation in flexor muscles. The propriospinal fiber system of the dorsolateral funiculi take the essential part in activation of CPG during SCS.*

Keywords: spinal cord, epidural stimulation, locomotion, central generator

1. Introduction

In organization of the locomotion activity, an important role belongs to the spinal central pattern generators (CPGs), which produce coordinated motor output. Under normal conditions, CPGs are under brain control, and sensory peripheral inputs can modulate their activity. From animal experiments it is known that the spinal cord isolated from the supraspinal influences and peripheral afferent feedback is capable to generate the stepping pattern. In clinical studies, it was shown that the patients with incomplete [1, 2] as well as with complete transection of the spinal cord at thoracic level [3, 4] can produce locomotor pattern after special training. These data have demonstrated the importance of peripheral input for initiation of stepping movements. Recently, we have obtained the experimental evidence for the existence of CPG in humans. It was shown that in patients with complete spinal cord lesion, the electrical epidural stimulation of the posterior surface above L2 spinal segment elicited the locomotor-like activity [5] In the present study, this phenomenon was further examined. We have used the epidural spinal cord stimulation (SCS) in order to evaluate

the origin of the rhythmic EMG activity produced by SCS and to verify the spinal structures responsible for initiation of the rhythmic activity.

2. Methods

Clinical studies. The capability of the lumbosacral cord to produce locomotor pattern in response to SCS was examined in eight patients with complete spinal cord injury (SCI). According to neurological criteria and ASIA classification, they were classified as ASIA A category with no motor or sensory functions below the lesion. Epidural stimulation was carried out with quadripolar electrodes (Medtronics) placed in the posterior epidural space at vertebral levels T11 through L1. The position of the electrodes was verified by fluoroscopy. Sometimes, we used the needle epidural electrode penetrated between Th11-Th12 vertebra. The frequency of SCS ranged from 0.3 to 40 Hz, the intensity ranged from 5 to 10 mA. The patients were placed in spine position on a comfortable table. EMG recordings of the *quadriceps*, hamstrings, *tibialis anterior* and *soleus* muscles in each leg were obtained by surface electrodes placed on these muscles. In addition to the EMG recordings, we used a position sensor to record the knee movements (Penny & Giles XM-180).

Animal experiments. The experiments were performed in the acutely and chronically spinalized cats. In the acute experiments, the cats were anesthetized with injection of kalipsol (30 mg/kg), then the intercollicular or anemic decerebration was performed. After laminectomy (L3- L7) the spinal cord was transected at Th10 level. The SCS was delivered by monopolar electrode located along the midline of dorsal surface of the spinal cord [6]. The EMG activity was recorded with bipolar wire electrodes inserted into the hindlimb muscles on both sides: *m.semitendinosus*, *m.rectus femoris* + *m.vastus lateralis*, *m.tibialis anterior* and *m. gastrocnemius*. The strength used was 10–400 mcA with pulse duration of 0.2 ms.

In another set of experiments, the dorsal columns (T 10) were dissected free from the spinal cord for their electrical stimulation. Besides, in some experiments the dorsal roots (L5, L6) were transected in order to put their central end on the stimulation electrodes.

In chronic experiments, after spinalization the epidural electrodes were inserted through the openings in the vertebrae into the dorsal surface of the L4-S1 segments or L5-L6 segments. In two cats, local lesion of the dorsal part of the dorsolateral *funiculus* between L5 and L6 segments (unilaterally) was performed 10 days prior to the experiment.

3. Results

The mapping of the spinal cord have shown that the effective region for eliciting locomotor-like activity is located above L2 spinal segment. It was found that the interval between the onset of high-frequency stimulation and the appearance of locomotor-like activity was 7 ± 1.2 s. After cessation of the stimulation, rhythmic EMG activity could persist for up to 8 s. It is necessary to note that in most cases we have observed the ipsilateral locomotor-like rhythmic activity. Only in two of our subjects the bilateral and coordinated alternating stepping movements of both legs were elicited. The stepping movements and EMG activity were observed at stimulation frequency of 20-50 Hz, pulse duration of 0.3-1 ms and strength of 8-12 V.

The pattern of activation of EMG activity in the leg muscles under constant frequency of 30 Hz and gradual increase of the stimulation strength was as following. In the beginning, a low amplitude tonic activity was elicited in the *quadriceps* and *adductor* muscles. Then the tonic EMG activity increased in amplitude and appeared also in the hamstring muscles. Further increase of the stimulus strength resulted in activation of *m. tibialis anterior* and *triceps surae* muscles. At last, tonic activity was replaced with rhythmic and locomotor-like EMG activity. This sequence was observed repeatedly in the same subject during one session, in different sessions, as well as in different subjects.

The process of forming the burst activity in leg muscles under SCS was investigated in detail. It was revealed that in response to low-frequency (0.5 Hz) SCS, the monosynaptic reflexes were evoked in *m. soleus* and *m. tibialis ant.* When the high-frequency (33 Hz) SCS was used, we have observed the same monosynaptic responses in the extensor muscle, while in the flexor muscle the polysynaptic responses were appeared with latency, which was 10-11 ms longer than for the monosynaptic reflexes. In accordance with these data, the bursting activity in extensor muscle was presented by the monosynaptic responses with modulated amplitude. In the contrary, in the flexor muscle the bursting activity consisted of the polysynaptic responses. It is interesting that polysynaptic responses were observed only during the flexion phase of the alternating movements. When high-frequency SCS elicited only the tonic activity in the flexor muscle, this activity was presented by the monosynaptic reflexes. This facts allowed us to conclude that locomotor-like activity in the flexor muscles under high-frequency SCS is the result of the switching the excitation from the monosynaptic to polysynaptic pathway.

In special experiments we have evaluated the role of the peripheral feedback in initiation of the locomotor-like activity during the high-frequency SCS. For this aim, we have used the ischemia of the leg. It was revealed that after twenty minutes of ischemia, the pattern of muscle activation under constant stimulation frequency of 30 Hz and progressively increased stimulation strength was the same as before the ischemia. This proves the intraspinal origin of the rhythmic activity produced by SCS. The ischemia resulted in decrease of the amplitude of the evoked EMG activity only. It is necessary to note that ischemia affects the proximal muscles greater than the distal muscles.

At the same time, it should be noted that proprioceptive reflexes (vibration) applied to muscle tendon during SCS are able to modify the tonic activity to burst one or to increase the amplitude of the burst activity. This shows that the afferent input can influence the rhythmic activity produced by SCS.

Thus, it may be supposed that rhythmogenesis of locomotor-like activity elicited by SCS is based on the interaction of generation of rhythmic activity (the mechanism intrinsic for the spinal cord) and the peripheral afferent feedback.

In order to verify the spinal structures mediating the effect of SCS to CPG, the experiments in spinalized cats were performed. It was found that as in humans the effective region for eliciting locomotor-like activity provoked by SCS is located at the upper border of the lumbar enlargement (L4-L5 segments). As in humans, in the beginning SCS evoked the tonic activity, which then was transformed to the burst one. The structure of responses to low-frequency SCS was different in the extensor and flexor muscles. In the extensor muscles, the response was monosynaptic, while in the flexor muscles both early and late responses were observed. The latency of the early response was 11 ms and the latency of late one - 110-150 ms. After cessation of SCS (5Hz), the late response activity continued for 3-4 seconds. Under high-frequency SCS, initiation of the rhythmic burst activity arised in flexor muscle as a consequence of interaction of the mono- and polysynaptic reflexes. The selective stimulation of the dorsal columns did not evoke the rhythmic locomotor-like activity in hindlimb muscles, probably, because it evoked the monosynaptic responses only. After unilateral section of dorsal column, the SCS applied above the site of injury evoked locomotor-like burst responses only in the muscles at the side of the intact dorsal column. The stimulation of the dorsal root (L5) did not elicit locomotor-like activity. In this case, only the early responses were observed.

The experiments with chronic local lesions of the dorsal part of dorsolateral funicili have shown that the epidural stimulation above the site of lesion did not evoke locomotor-like activity. When we stimulated the dorsal surface of the spinal cord one segment below injury, we obtained well-coordinated rhythmic locomotor-like activity. This may evidence in favor of important role of the propriospinal system in initiation of the locomotor-like activity produced by SCS.

4. Conclusion

The data in favor of the existence of CPG in humans are coming from: the capacity of the paraplegic patients to produce the stepping movements after a course of special training [2] and possibility to evoke the stepping movements by the vibration applying to muscle tendon in normal subjects with unloaded legs suspended in horizontal position [7]. Recently, we have presented the data showing that spinal cord stimulation of the upper segments of the lumbosacral cord in complete paraplegics elicited locomotor-like EMG activity and stepping movements. In the present study, the mechanisms of initiation of the locomotor-like activity produced by SCS were investigated. The epidural stimulation applied to the dorsal surface of the spinal cord initially activates the system of fibers of the dorsal column and dorsolateral funiculi. The tonic activity, which appears first under progressively increased strength of simulation, consisted of monosynaptic reflexes. It may be suggested that monosynaptic reflexes are elicited due to antidromic activation of afferent fibers in the dorsal columns. The locomotor-like activity appeared when the intensity of stimulation was approximately doubled. In this conditions the reflex responses structure in the flexor muscles were changed. The monosynaptic reflexes were inhibited and the burst of the EMG activity was composed with the polysynaptic responses. It may be supposed, that with the increasing of the stimulation intensity, polysynaptic responses arise as a result of propriospinal neurons activation by the SCS excited dorsolateral funiculi fibers. The fact that SCS provoked in the patients basically unilateral stepping, may evidence in favor of predominant of activation of the unilateral dorsolateral funiculi fibers and consequently, unilateral propriospinal neurons. The results of experiments with the local lesion of the dorsal part of dorsolateral funiculi supports the opinion about the substantial role of the dorsolateral funiculi propriospinal fibers in the initiation of locomotion under SCS.

On the base of data received it may be supposed that SCS antidromically activates the uninjured parts of primary afferents branches in the dorsal columns and their collaterals. Through this route excitation can monosynaptcally activate motoneurones and polysynaptically interneurones of the dorsal horn base. It is possible, that initiation of locomotor movements is realized by means of long propriospinal fibers system in the dorsolateral funiculi. These fibers, connected with the interneurones of the dorsal horn base, apparently activate the gray matter intermediate zone neurons. As the neurons of VI-VIII Rexed layers discharges rhythmically during fictive locomotion, they most probably are the components of CPG [8] and may be activated through the propriospinal system of the spino-cerebellar tract.

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