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Lecture

Central pattern generator in the spinal cord

—— From the point of view of rehabilitation ——

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Abstract

Rhythmic activities such as walking are regulated by neural organizations called central pattern generators (CPGs). CPGs become autonomous in function when interrupted from higher control centers. "Decerebrate cats" whose spinal cord has been transected at the brain stem can walk on a treadmill. Interneurons in the CPG act as rhythm-generators that regulate alternating motions of extensor and flexor. CPGs are distributed throughout the spinal cord in laboratory animals. It is suggested that the CPG might also exist in the human spinal cord. This indicates a potential benefit of retraining on recovery from spinal cord injury. Rehabilitation of patients with spinal cord injury can be re-evaluated from the point of view of CPG.

Key words: central pattern generator, locomotion, interneuron, paraplegia, spinal cord injury, rehabilitation

Introduction

We can usually conduct rhythmic behaviors such as walking, chewing, and breathing almost unconsciously. These movements are, however, not totally independent of control from the brain; we can control these movements voluntarily. It can be said that these behaviors consist of two components: an inherent rhythmic property, and supervisory regulating control from the brain. The rhythmic activity of these patterned behaviors is considered to be an inherent property of nerve networks in the brainstem and spinal cord.

The neural organizations of these rhythmic activities are called central pattern generators (CPGs) (Graham-Brown, 1911, 1914). CPGs are identified not only in the vertebrate nervous system, but also in invertebrate (for example, the lobster and snail) nerve ganglia for feeding and walking (Staras et al., 1998; Selverston et al., 1982). Alving (1968) first identified pace maker neurons that produce rhythmic activity in Aphysia ganglia. The rhythmic activity by CPGs is a functional property that is commonly seen in the neural organization of the animal kingdom.

The locomotor CPGs in the spinal cord have been studied in vertebrates including amphibians and mammals, among which the cat is most frequently used for experiments. Locomotor CPGs are centers of rhythmic alternation of right-left limb movement as well as flexor-extensor muscle contractions. CPGs are centers for the coordinated stepping that continues smoothly without any conscious control. The most remarkable demonstration of CPGs in vertebrates is the experiment by Sherrington (1910), in which he showed that "decerebrate cats" could walk. "Decerebrate cat" or "spinalized cat" means a cat whose spinal cord has been transected at the brain stem, and accordingly, has no fiber connection with the brain. Though no information can be transmitted from the brain, the decerebrate cat can perform, albeit rudimentary in pattern, walking behaviors. If assisted, a decerebrate cat can walk almost normally on a treadmill. Subsequently Graham-Brown (1911, 1914) demonstrated that a cat with transection of the spinal cord at the T12 level and, in addition, deafferentation by cutting off sensory nerves innervating hind-limb muscles, could exhibit walking behaviors, indicating that the

CPG for hind-limb locomotion is located in the lumbar part of the spinal cord.

It is suggested that neural networks similar to the cat CPG also exist in the human spinal cord (Dimitrijevic et al., 1998). It has long been believed hat the afferent reflexes are the basis on which motor movements are produced. However, instead of the reflex concept, the "motor program" has recently emerged as a new concept for producing motor behaviors (Marsden et al., 1984). The "motor program" is defined as the neural mechanism of patterned muscle contraction independent of peripheral afferents. This notion contributed to the formation of the CPG concept.

If CPGs exist in the human spinal cord, the training of motor activity through CPGs is critical in the rehabilitation of paraplegic patients with spinal cord injury (SCI). There might be a possibility that paraplegic patients could recover by activating CPGs of the spinal cord. In this respect, the effect of treadmill training on the walking of decerebrate cats is very suggestive: patients with SCI might recover from paraplegia by treadmill training. Along this line, body weight-support treadmill training has already been tried with patients with SCI.

In this lecture, I want to explain the CPG in mammals including humans, and emphasize the great potentiality of CPGs utilized for the rehabilitation of patients with SCI.

Concept of CPG

There are two kinds of locomotion patterns in mammals: a quadrupedal gait as seen in the rat and cat, and bipedal gait unique to humans. Quadrupedal locomotion shows a well-coordinated movement of forelimbs and hind limbs. The bipedal human seems to have maintained a reminiscent mechanism of quadrupedal stepping in the coordinated patterns of moving the arms and legs in walking. Basically, locomotion means the left-right as well as flexor-extensor alternation of the limbs during walking.

As described above, Graham-Brown demonstrated the existence of neural networks for hind-limb walking in spinal cord segments below the transection at the thoracic level in the cat. This neural network is independent of brain control, and serves as a center for generating the autonomic and rhythmic movements of hind limbs. This neural network is CPG. Rhythmic activities of the CPG underlie the left-right and flexor-extensor alternation of the hind limbs. Though morphological evidence for the CPG remains elusive, the existence of CPGs is functionally confirmed in the lumbar spinal cord. Graham-Brown (1911) proposed the "half-centers" hypothesis as a model of CPG (see below). According to this hypothesis, rhythmic motor activity is generated in 2 pools of interneurons on each side of the spinal cord. One half acts as the center for the extensor, and the other half the center for the flexor of the limb. The two half centers interact with each other by reciprocally inhibiting the other one: the extensor half center activates extensor motoneurons by interneurons, while inhibiting flexor motoneurons, and the flexor half center acts conversely, i.e., it activates flexor motoneurons, inhibiting extensor motoneurons by interneurons in the ventral horn (Graham-Brown, 1914).

As already stated, CPGs for patterned movements other than locomotion exist at a higher level in the brain stem, which includes breathing, chewing, and swallowing. CPG neural circuits might be included in the nuclei that innervate each responsible organ in the brain stem (Jordan et al., 1992; Marder et al., 1996).

Localization of CPG in the spinal cord

A cat with transection of the spinal cord at the thoracic level shows coordinated alternating movements on a treadmill (Fig. 1). The locomotion shows well patterned left-right and flexorextensor alternation (Forrsberg et al., 1980; Barbeau et al., 1987). Even when the muscle action was suppressed by curare, electrophysiological locomotor rhythm could be recorded in the corresponding ventral roots (this is called "fictive locomotion") (Rybak et al., 2006a). Next, the *in vitro* preparation of isolated spinal cord was developed. The spinal cord is isolated from the body in either a condition in which the hind-limb muscles are attached or no organs other than roots accompany to the spinal cord. The isolated spinal cord is bathed in Ringer solution. The function of the spinal cord can be maintained almost normally for several hours, during which the stimulation-response can be recorded electrophysiologically. The isolated spinal cord can be stimulated by serotonin (5-HP), NMDA (N-methyl-D-aspartate), or dopamine added to Ringer solution. The isolated

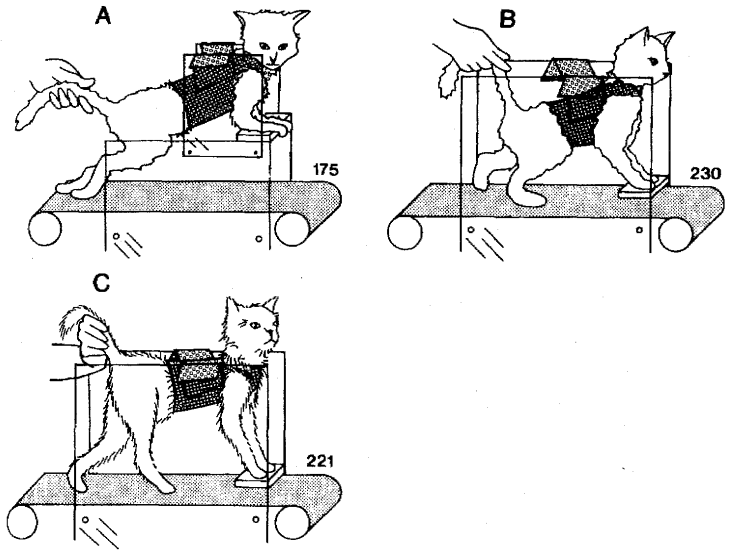

Fig. 1 Drawing of treadmill locomotion of a cat with spinal cord transection. (A) Without weight support, the hind paws would drag on the treadmill. With weight support, the cordotomized cat could be in a paw-position (B) or digit-position (C) of hind limbs that were flexed (B) or properly extended (C). (Reproduced from Exp Neurol 76, Smith et al.: Locomotion in exercised and nonexcercised cats cordotomized at two or twelve weeks of age, pp. 393–413, 1982, with permission from Elsevier)

spinal cord can be transected at varying levels to examine at what level the CPG exists by stimulation-response recording. The actual experiment goes as follows: spinal cord isolated from a mouse is bathed in Ringer solution, CPGs in the isolated spinal cord can be stimulated with transmitters or modulators added to Ringer solution, as described above, and usually the neural response from the spinal cord is recorded at the ventral roots or in the corresponding muscles. The thoracosacral spinal cord preparation of neonatal mice with the attachment of hind limbs shows alternative electrical responses in the common peroneal and tibial nerves, innervating the tibialis anterior and gastrocnemius muscles, respectively. This alternative pattern of impulses is the same as seen in intact adult mice (Pearson et al., 2003). In the spinal cord preparation in which all accompanying organs other than roots were removed, recording was performed in L2 ventral roots on both left and right sides, or in the ipsilateral L2 and L5 ventral roots: the former is the recording of alternating movements of left and right hind limbs, whereas the latter is the recording of flexor and extensor alternation. Both patterns of responses are the same as those seen in the locomotion of intact adult mice (Whelan et al., 2000).

It is interesting that a similar response of locomotor-like activity can be obtained in the isolated spinal cord by electrophysiological stimulation at the cauda equina (Gordon et al., 2006). The recordings from L2 on left and right sides show the well-coordinated left-right alternative responses, and the recording from ipsilateral L2 and L5 show the flexor-extensor alternation of the hind limbs. On the other hand, the recording from the C8 ventral roots on left and right sides shows the left-right alternation of the forelimbs. The recording from the ipsilateral C8 and L2 shows the alternating movements of forelimbs and hind limbs (Fig. 2). The fact that stimulation of the cauda equina elicits locomotor-like CPG responses is important from the point of view of rehabilitation. Electrical stimulation could be applied to cauda equina to facilitate the locomotor ability of paraplegic or tetraplegic patients with SCI (Gordon et al., 2006).

CPGs are probably not confined to limited areas such as enlargement of the spinal cord, but distributed throughout the spinal cord. This finding was obtained in the experiment in which divided spinal cord segments were studied for recording from the ventral roots. The spinal cord transected at the mid-thoracic level shows left-right alternative responses of ca. 20-second intervals from S2 ventral roots.

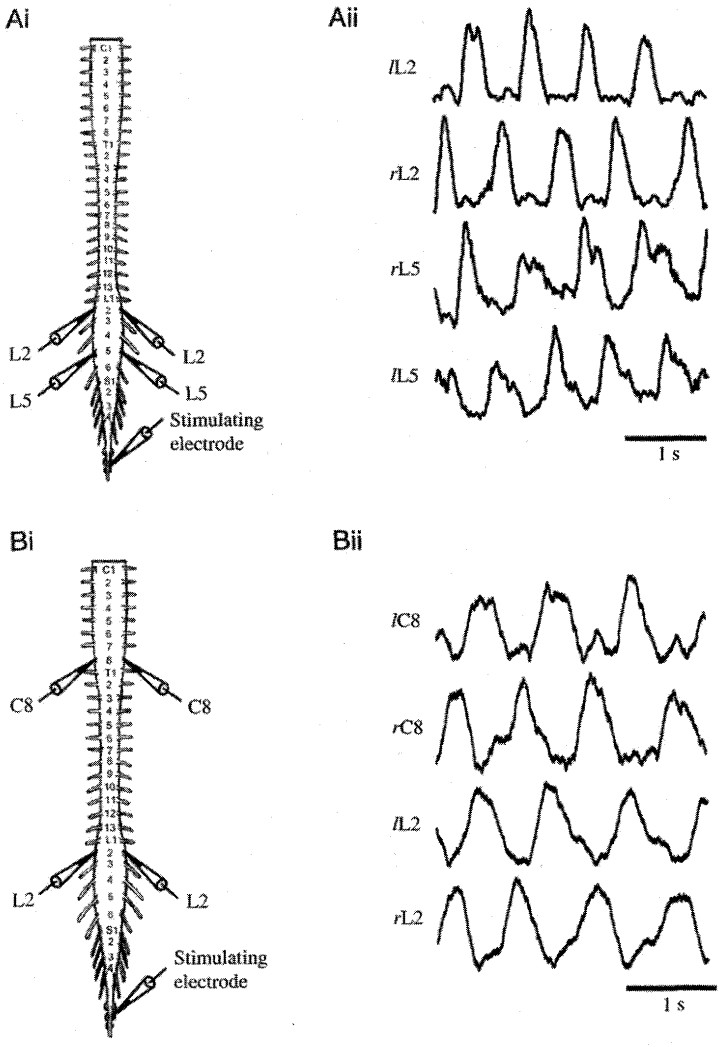

Fig. 2 (Ai) Electrical stimulation of the cauda equina can evoke the lumbar locomotor-like activity. Neurogram traces were recorded from the 2nd and 5th lumbar ventral roots (L2, and L5, respectively). (Aii) Neurogram traces of left and right lumbar ventral roots (*l*L2, *r*L2, *l*L5 and *r*L5) show the left-right and flexor-extensor alternation.
(Bi) This scheme shows the recording from the 8th cervical (C8) and 2nd lumbar (L2) ventral roots following electrical stimulation of the cauda equina. The neurogram traces show the alternation of cervical and lumbar segments, that is, the locomotion of forelimbs and hind limbs. (Reproduced from J Exp Biol 209, Gordon et al.: Deciphering the organization and modulation of spinal locomotor central pattern generators. pp. 2007–2014, 2006, with permission of the Company of Biologists)

The shorter lumbosacrococcygeal spinal cord cut between L3/L4 also shows alternative rhythmic responses of longer (ca. 40 seconds) interval at the S2 ventral root. Even a shorter sacrococcygeal spinal cord cut at L6/S1, and a spinal cord segment between S1 and S4 produced by cutting at L6/S1 and S4/Co1 show response patterns similar to spinal cord preparations cut at L3/L4. Even the tiny coccygeal spinal segment cut at S4/Co1 shows an alternative response from the Co1 ventral root. Even when the spinal cord transected at S1/S 2 was further split mid-sagittally, the alternating response can be obtained from Co1 (Fig. 3). These findings indicate that the CPG neural circuits are distributed throughout the spinal cord, and that the CPGs located at a higher spinal cord level might drive the frequency of lower-situated ones (Gabbay et al., 2002).

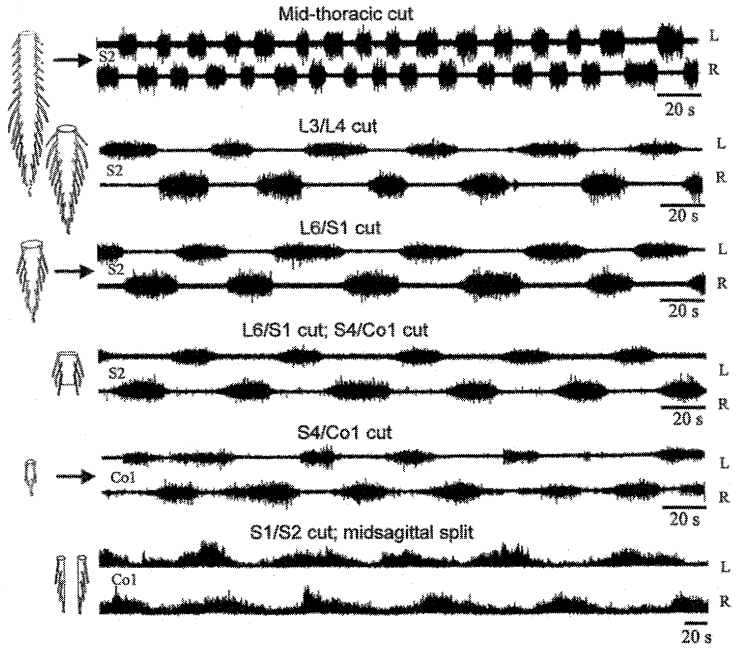

Fig. 3 CPGs are distributed in the sacrococcygeal spinal cord segment. The isolated spinal cord was bathed in the solution containing 5 μM noradrenalin and 4 μM N-methyl-D-aspartate (NMDA). The spinal cord cut at mid-thoracic level showed high-frequent left-right alternating discharges recorded from the 2nd sacral ventral roots (S2) (two traces at the top). The spinal cord segment cut at L3 an L4 (L3/L4 cut) showed low-frequent left-right alternating discharges. The smaller spinal cord segment cut at L6/S1 and S4/Co1 (L6/S1 and S4/Co1 cut) exhibited a similar pattern of discharges from S2. Even the coccygeal segment cut at S4/Co1 (S4/Co1 cut) showed an alternating pattern recorded from the Co1 ventral roots. The half-split spinal cord segments produce alternating patterns recorded from the Co1 ventral roots (two traces at the bottom). (Reproduced from J Neurophysiol 88, Gabbay et al.: Pattern generation in caudal-lumbar and sacrococcygeal segments of the neonatal rat spinal cord. pp. 732–739, 2002, with permission from the American Physiological Society)

Neural model of CPG

At present, CPG is a functional concept. Neural networks of the CPG have not been identified morphologically. Rhythmic activity is the most distinct functional property of the CPG. A certain neuron of the CPG neural circuits should autonomously generate rhythmic impulses that activate or inhibit related motoneurons in an integrated and coordinated manner. It has been suggested that the rhythmic impulses are probably produced in the interneurons of the CPG. Developmentally, four different groups of interneurons have been proposed, V0, V1, V2, and V3, in the spinal cord. Among them, the V0-belonging interneuron named Hb9 is a candidate for a rhythm-generating neuron. This interneuron is located in the medial part of the VIII area in the anterior horn of the upper (L1-L3) lumbar cord (Goulding et al., 2005; Gordon et al., 2006). Other interneurons involved in rhythmic activity are EphA4 (ephrin receptor A4) cells (Angel et al., 2005; Butt et al., 2005). Target deletion of the gene EphA4 or ephrin ligand B 3 results in gait disturbance (Coonan et al., 2001; Yokoyama et al., 2001). The EphA4 cells are located lateral to the Hb9 cell cluster in the ventral horn of the spinal cord (Kiehn, 2006).

The model proposed by Rybak et al. (2006b) shows that the CPG is composed of 2 half-centers for extensor and flexor muscles. Each half center contains rhythm generator interneurons and pattern formation interneurons. In addition, each rhythm generator and pattern formation interneuron has an inhibitory interneuron that suppresses the excitation from the other half. Rhythm generator inter-

neurons in the flexor half excite the pattern formation interneurons of the same half, while, at the same time, inhibiting the rhythm generator interneurons of the extensor half through the corresponding rhythm generator-inhibitory neurons, and vice versa for the extensor half center. For output, pattern formation interneurons in the flexor half interneuron excite the motoneurons of the flexor half (Fig. 4).

Rhythm-generator interneurons are driven by the higher center in the midbrain. The mesencephalic locomotor region (MLR) activates reticulospinal neurons of the lower brain stem (Garcia-Rill et al., 1987). Above the mesencephalon, cerebellum, basal ganglia, and

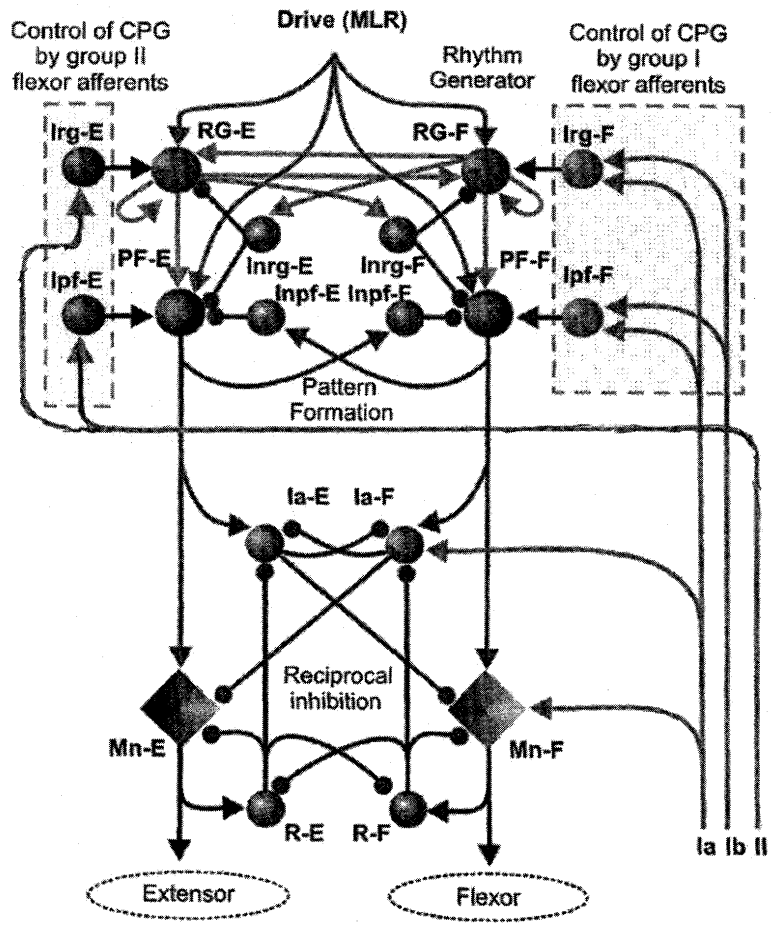

Fig. 4 This diagram shows the neural circuit model of the half-center CPG concept proposed by Rybak et al. 2006 The excitatory drive (tonic excitation) is generated in the midbrain center called the midbrain locomotor region (MLR) and transmitted to rhythm-generator interneurons (RG) of the spinal cord. RG-E and RG-F designate the rhythm-generator for the extensor and rhythm-generator for the flexor, respectively. Excitatory rhythmic stimulation from RG is transmitted to the neurons as follow: RG of antagonist muscles, associated inhibitory interneurons (Inrg-E, and Inrg-F), and pattern-formation interneurons (PF) of agonist muscles. Excitation of Inrg-E and Inrg-F inhibits RG and PF of antagonist muscles. Excitation of PF is transmitted to inhibitory interneurons of pattern formation (Inpf-E and Inpf-F) of antagonist muscles, and motor neurons (Mn) of agonist muscles. Excitation of motor neurons can be modified via Renshaw cells for extensor and flexor (R-E and R-F, reespectively), and finally conveyed to activate corresponding extensor or flexor muscles. Inputs from musculo-tendinous receptors including muscle spindle annurospinal endings (Ia) and Golgi tendon organ (Ib) of flexor side are transmitted to hypothetical interneurons related to rhythm generator (Irg-E and Irg-F), and hypothetical interneurons related to pattern formation (Ipf-E and Ipf-F) of the flexor side. Inputs from muscle spindle flower-spray endings (II) on the flexor side are conveyed to the Irg-E or Irg-F and Ipf-E or Ipf-F of the extensor side. These inputs excite corresponding rhythm-generator and pattern-formation interneurons. In addition, inputs from Ia of flexor side stimulate the motor neuron itself and inhibitory interneuron specific to Ia (Ia-E and Ia-F) of the flexor side. (Reproduced from J Physiol 577 (Pt 2), Rybak et al.: Modelling spinal circuitry involved in locomotor pattern generation: insights from the effects of afferent stimulation, pp. 641–658, 2006, with permission from Blackwell Publishing)

cerebral cortex are centers to control the CPGs. The cerebral cortex is the center of voluntary movements that triggers behaviors including locomotion. The cerebellum and basal ganglia are involved, together with the cerebral cortex, in the complex tuning and controlling of locomotion. All together, the supraspinal centers control the activity of CPGs in the spinal cord, maintain equilibrium during locomotion, adapt limb movements to external conditions, and coordinate locomotion with other motor activities (Orlovsky, 1991). The rhythmic activity of interneurons is controlled by the supraspinal influences in the normal condition. When supraspinal control is lost, CPGs can produce their own characteristic rhythm under appropriate stimulation.

Influence of sensory afferents on locomotor CPGs

The isolated spinal cord experiment indicates that CPGs can generate motor activity without peripheral feedback. However, peripheral afferents are important in modifying the motor output from the CPG. Though they are extrinsic to the CPG system, peripheral afferents contribute to the adaptation of motor behaviors. Peripheral afferents are not causative but regulative to the CPG function.

Three roles of afferent feedback have been proposed in the CPG function: the first is strengthening the CPG activities of load-bearing muscles including hind-limb extensor muscles, the second is controlling the timing of motor output in accordance with the movement and force, and the third is facilitation of phase transition of the rhythmic movement (Pearson, 1993).

Afferents from muscle spindles (Ia) and Golgi tendon organs (Ib) of extensor muscles control the amplitude, duration, and timing of ipsilateral extensor activity (Guerin et al., 1995). The low threshold cutaneous receptors (for example, Meissner corpuscles and Merkel-neurite complexes) have an effect on locomotion in a phase-dependent manner. That is, the stimulation of cutaneous afferents from the dorsum of the foot elicits extensor muscle contraction during the stance phase, and produces flexor muscle contraction during the swing phase of the hind limb (Pearson, 1993). Rybak et al. (2006b) produced a model for the contribution of afferents to CPG function (Fig. 4). The contribution of afferents is an important basis for retraining of paraplegic patients with SCI in rehabilitation.

The existence of CPGs in humans

The first report was made about 50 years ago concerning the alternating extension and flexion movements in the individuals with complete SCI (Kuhn, 1950). Subsequently, the rhythmic contraction of lower limb extensor muscles was reported in an individual with complete SCI (Bussel et al., 1996). This activity was modulated by peripheral afferent stimulations. Electrical stimulation of the spinal cord produced extensor patterns for standing and stepping postures in patients with complete SCI (Dimitrijevic et al., 1998; Jilge et al., 2004). Locomotor-like electrical responses could be obtained in individuals with complete SCI, when stepping-related sensory cues were given to the externally assisted-leg (Harkema et al., 1997). However, these responses were lower than the level at which the leg can move independently.

Recently, the stepping of one leg was observed with an assistance of the other leg, albeit full weight bearing was not achieved, in patients with complete SCI after several months of locomotor training (Behrman et al., 2000). In an experiment with healthy individuals, afferent input from load receptors and hip joints plays an important role in leg muscle activation during locomotion (Dietz et al., 2004). The input from load receptors means proprioceptive afferents from extensor muscles and from mechanoreceptors in the foot sole. These afferent activities contribute to regulate and modulate locomotor movements (van Wezel et al., 1997). These studies suggest that locomotor-related pattern generators might exist in humans. This indicates the potentially beneficial effects of retraining on recovery from paraplegia in patients with SCI. In this respect, rehabilitation should be encouraged for patients with complete SCI.

Retraining of locomotor behaviors

It is tempting to consider that CPGs should be utilized for locomotor rehabilitation in patients with spinal cord injury. Experiments with the spinal cord-injured cat suggest that there is a possibility of using CPG circuits to restore locomotor function. The use of CPGs is a promising field of locomotor rehabilitation.

Adult cats with transection of the spinal cord at T13 showed poor hind-limb stepping on a treadmill. However, after 3-4 weeks of daily treadmill training, they demonstrated a near-normal pattern of locomotion. Those cats could adjust stepping to changes in the speed of the treadmill by the end of the training. At the beginning of the experiment, cats were weight-supported at the tail, and gradually released from the support to sustain their own body weight (Barbeau et al., 1987). This experiment also reported that the intraperitoneal administration of clonidine (noradrenergic agonist) enhanced the recovery of locomotion during treadmill walking. In another experiment, embryonic locus ceruleus and brain stem raphe were transplanted into the T 12–13 segments of rats with transection of the spinal cord at T8–9. As stated above, serotonin and noradrenalin are stimulants of spinal CPGs. Six weeks after surgery, the tibialis anterior and gastrocnemius muscles contracted alternately. Immunohistochemistry showed that there was a rich monoaminergic reinnervation in the lumbar enlargement of the spinal cord. This study indicates that combined transplantation and treadmill training therapy will further enhance the recovery of locomotor activity of paraplegic patients with SCI (Feraboli-Lohnherr et al., 1997).

The treadmill training studies suggest that the CPG might have use-dependent plasticity activated by forced walking on the treadmill. Forced treadmill training conveys cutaneous and muscle inputs to the CPGs and helps the CPGs integrate the information for output of motor activities.

Though it is highly probable that the CPG exists in the human spinal cord, a direct extension of the tetrupod CPG concept to the biped human is problematic. An upright bipedal gait is unique to humans, and probably more dependent on supraspinal control. Nevertheless, CPGs might be the most promising target for the active locomotor training of paraplegic patients with SCI. The effects of body-weight supported treadmill training on paraplegia should be explored on a larger scale. A study in which patients with incomplete SCI received an training of treadmill walking with 40% body weight support by an overhead frame demonstrated the immediate normalization of the gait activity of the patients. Body weight support is absolutely necessary in treadmill training (Visintin et al., 1989). Wernig reported the results of the training of 8 patients with chronic incomplete SCI who received treadmill training for 6 weeks to 20 months with 40% body weight support. Electromyography showed an increase of the activity in extensor and flexor muscles of the lower limbs during locomotion. The authors reported in another study that 33 of 36 patients with incomplete SCI could walk independently after treadmill training for 3 to 20 weeks. However, those with functionally complete SCI showed no improvement (Wernig et al., 1995).

Treadmill walking has also been reported to be beneficial in the rehabilitation training of stroke-hemiplegic subjects (Hesse et al., 1995; Hassaid et al., 1997). Body weight support-treadmill training was very effective for gait improvement in 100 patients post-stroke. Body weight-support training is much more effective in improving balance, speed, and endurance in locomotion, than full-weight bearing therapy (Visintin et al., 1998).

Unfortunately, it is not known to what extent the CPGs can contribute to the locomotory improvement of patients with complete SCI. The distinct effect of body weight support-treadmill training to patients with incomplete SCI might be due merely to plastic changes of nerves preserved after spinal cord injury. To what extent spinal CPGs might contribute to the locomotory improvement in complete SCI is an important problem in the field of the rehabilitation of patients with SCI. On the other hand, patients with chronic SCI who received locomotor training exhibited greater mobility than a control group with conventional rehabilitation (Wernig et al., 1995). Locomotor training is a new rehabilitation approach. As described above, sensory inputs conveyed to the spinal cord during locomotor training are considered critical for the improvement of locomotory activity.

Future problems

The existence of CPGs has been recognized in the human spinal cord. The study of CPGs revealed that the spinal cord might be more plastic in nature than ever believed. An understanding of CPGs should lead to effective locomotion training in the rehabilitation of patients with SCI.

CPGs are a functional unit of the neural circuit in the spinal cord. The rhythmic ac-

tivity is generated by interneurons. Motoneurons are the final output of impulses produced by interneurons. Morphological as well as physiological evidence should be accumulated to identify rhythm-generating interneurons in the spinal cord. It is probable that, albeit the CPGs might be distributed throughout the spinal cord, the most developed networks of CPGs might be located in the cervical and lumbar enlargements.

CPGs are not isolated units independent of other neural networks, but dependent on higher level control including the brain. When the spinal cord is transected, the CPGs below the transection become free from these supraspinal controls. It seems that CPGs in the mammalian spinal cord isolated from supraspinal controls need appropriate stimuli to produce rhythmic activity.

How to stimulate the CPGs below the transection level in the spinal cord might be the most critical problem for retraining patients with SCI. Peripheral afferents might be one of the major components to stimulate CPGs. Treadmill training contributes to the increase of sensory inputs from the cutanenous as well as muscular sensory organs. The finding that neuromodulators and transmitters such as noradrenalin and serotonin promote CPG function is another important aspect of CPG stimuli. This finding indicates that there would be a possibility to pharmacologically manipulate stimuli to activate CPGs for patients with SCI. How CPGs can be stimulated, and what kinds of stimuli are appropriate are major subjects of research in the rehabilitation of patients with SCI.

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