Lecture

Clinical aspects of the central pattern generator in the human spinal cord

Chizuka IDE *Professor, Department of Occupational Therapy, Faculty of Nursing and Rehabilitation, Aino University. Director, Aino Institute of Regeneration and Rehabilitation*

Norihiko NAKANO *Associate Professor, Aino Institute of Regeneration and Rehabilitation, Aino University.*

Yoshiyasu NAKAI *Technical Associate, Aino Institute of Regeneration and Rehabilitation, Aino University.*

Abstract

The central pattern generator (CPG) in the spinal cord has been proposed as a functional unit involved in the rhythmic alternating locomotor activity of the lower limbs in humans. If the CPG can be activated by external stimulation, patients with spinal cord injury (SCI) will derive a great benefit from rehabilitation in which CPG activity is stimulated by treadmill training and/or electrical stimulation of the spinal cord. In this short overview, we focused on evidence for the existence of CPG in the human spinal cord, and discussed the clinical findings that indicate the benefits of rehabilitation for the patients with SCI. It should be emphasized that the activation of CPG is vital in designing rehabilitation programs regarding the locomotor activity of patients with SCI.

Key words : central pattern generator, spinal cord injury, rehabilitation, treadmill training, clinical efficiency

Introduction

In our previous communication, we overviewed studies dealing with basic properties of the central pattern generator (CPG) in the cat spinal cord, with emphasis concerning its implication to the rehabilitation of patients with spinal cord injury (SCI) (Ide, 2006).

In general, the CPG is a functional unit to regulate rhythmic alternating movements such as chewing, breathing, swallowing, and walking. The CPG is considered distributed throughout the brainstem; CPGs for chewing, breathing, and swallowing are in the upper brainstem, whereas those for walking are at the lower level, i.e., in the spinal cord. CPGs in the spinal cord are functional neural circuits that regulate the alternating hind limb movement during locomotion in lower mammals including the rat and cat. Various models of CPG neural circuits have so far been proposed to explain the neural mechanism of rhythmic movements based on its physiological prop-

erties. However, there has been no study concerning the cellular organization of neural circuits of the CPG.

The CPG is considered to be the control site for the locomotion even in the human spinal cord. The spinal cord CPG is important in that it has profound relations with the rehabilitation of patients with SCI. If the CPG in the spinal cord can be properly activated by some rehabilitative techniques, wheelchair-bound patients with SCI might derive a great benefit: at the optimal level, they might possibly be freed from the wheelchair, and, further, be able to walk with a unilateral cane or bilateral braces.

It has been recognized that the afferent inputs from mechanoreceptors within the skin and joints are critical for CPG function. This fact is important in considering the rehabilitation of patients with SCI. The afferent inputs are relayed to the interneurons that finally connect with the motor neurons to generate locomotion. Rossignol et al. (2005)

conducted an extensive review on sensori-motor interaction and the CPG in locomotion. Dietz (2003) reviewed the CPG in terms of rehabilitative therapy.

In this short review, we will look at the current status of studies on the CPG in the human spinal cord. It is still a matter of debate as to what extent the CPG in the human spinal cord contributes to locomotor activity. However, some clinical cases indicate that the CPG seems to be functioning in subjects with complete or incomplete SCI. We will first describe some CPG models in animals, and then introduce several studies concerned with the contribution of the CPG to the rehabilitation of SCI patients.

1. CPG models in animals

The CPG was first proposed by Brown (1911), who showed that rhythmic stepping activity is observed in the acute spinal cat, and that such rhythmic activity does not depend on reflexes but persists even after peripheral sensory nerve transection (deafferentation). Similarly, such alternating activity can be observed after curarisation, i.e., after the loss of Ia afferent by the inactivation of the muscle contraction (Perret et al., 1976).

The CPG has been extensively studied in lower mammals (Grillner and Wallen, 1985). It is regarded as a behavior-generating motor center in a broad sense. Also it has been well recognized in alternating motions of swimming from lower vertebrates such as the lamprey (Grillner, 2006). In mammals, locomotion is controlled by the CPG in the spinal cord. The mammalian CPG has mainly been studied using spinal cats, in which the spinal cord was isolated from the brain by transection at the upper brainstem, including the midbrain. The spinal cat can walk using its hind limbs following training on a treadmill. The spinal cat is a typical model for the existence of CPG in mammals. Spinal kittens can, after practice, walk on a treadmill in a fashion very similar to that of normal cats. Kittens exhibit a marked plasticity regarding CPG neural circuits. Adult cats, as described above, show improved hind limb locomotion by treadmill training. Though the afferent input is vital to regulate CPG activity, spinal cats, even after severing all afferent inputs, can generate locomotor-like activity that are recorded electro-physiologically from the anterior root as the rhythmic activity in agonist and antagonist muscles of the hind limbs. This phenomenon is called "fictive locomotion" (Pinter and Dimitrijevic, 1999).

Grillner (2006) conducted a detailed review concerning basic properties of the CPG from lower vertebrates to mammals. In this review, he discussed the model of operation of CPG networks, and considered the neural mechanisms through which they are selected and activated. He has proposed a new concept of the "circuitry doctrine", the core unit of neuronal circuitry that explains the central motor program for animal behavior. He considers this concept as a new basic theory for central nervous system function. The discovery of central motor generators has provided crucial insight into the existence of one prototypic set of neural circuits. Locomotion is an alternating behavior generated by neural rhythmic activity. In locomotion, hundreds of muscles are coordinated with precise timing. In all vertebrates, the CPGs for locomotion are located in the spinal cord and are controlled by descending inputs from specific locomotor command region in the brain stem.

Frigon and Rossignol (2006) have described a concept that the spinal cord neural circuitry consists of separate modules (cores), with each module including an apha motoneuron controlling one muscle, a Renshaw cell, and Ia and Ib interneurons. Each module is driven by its respective CPG and by reflex feedback. This concept shows that interneurons play a central role in CPG activity. Along the same line, Yakovenko et al. (2007) have proposed the propriospinal hypothesis, and shown the benefits of propriospinal neuron stimulation. Microwires were implanted into the intermediate and ventral gray matter of T10–12 segments 2–3 weeks after spinal cord transection at T8–9. Intraspinal microstimulations were delivered during open-field locomotor tests. This stimulation significantly increased BBB scores beyond those of control tests. These results support the propriospinal hypothesis: neuronal activity elicited in thoracic spinal segments caudal to a complete spinal cord transection may propagate caudally and activate the locomotor CPG.

Dietz and Colombo (2004) show that the pattern of locomotion depends on the level of the lesion: the higher the level of spinal lesion the more normal the pattern of locomotion. This suggests that neuronal circuits under-

lying the locomotor pattern generator in humans is not restricted to any specific level of the spinal cord, but extends from the thoracolumbar to cervical levels. Similarly, functional recovery including the BBB score and EMG amplitude of the tibialis anterior was greater in T8– than in L2–injured rats (Garcia-Alias et al., 2006). This indicates that L 2 injury causes severer disruption of the CPG, with no CPG replacement available.

Transmitters such as catecholamine and serotonin have an effect on CPG activity. The implantation of embryonic raphe cells into the injured spinal cord generates improved patterns of locomotion. Histologically serotonin-releasing neurons within raphe tissue survive and extend axons to the adjacent segment of the spinal cord (Gimenez y Riotta et al., 2000). Similarly, the administration of catecholamine and serotonin with their respective receptor agonists generates locomotor-like movements in chronic spinal cord mice, and treadmill training enhances locomotion (Guertin, 2004). The receptors of serotonin, $5-HT_{1A}$ and $5-HT_7$, are responsible for locomotion. An agonist of both $5-HT_{1A}$ and $5-HT_7$ was used. Antagonist treatment reduced movements of locomotion. $5-HT_{7-/-}$ shows no improvement of locomotor activity (Landry et al., 2006). The administration of a $5-HT_{1A/7}$ receptor agonist activates the CPG of external urethral sphincter, thus improving the micturition of SCI patients (Dolber et al., 2007).

Frigon and Rossignol (2006) have emphasized the importance of sensory input to regulate CPG activity. Sensory information from cutaneous and muscle receptors has a strong impact on the timing and amplitude of locomotor activity. Stretch and load receptors (Ib fibers from the Golgi tendon organ) provide excitatory feedback to motoneurons during locomotion.

Van de Crommert et al. (1998) pointed out the importance of locomotion-related sensory input to activate and/or regulate the spinal locomotion-associated circuitry. Treadmill training providing strong sensory inputs during locomotion is a powerful treatment for spinal cord-injured cats and humans.

2. CPG activity in humans

(1) Locomotion in humans
CPG activity is larger in quadripedal animals than in bipedal humans. In humans, the forelimb (arm) is not for locomotion, but for skilled movements. In addition, the hind limbs play a role in up-righting the body. This change markedly decreased the locomotive function of the hind limbs in humans. Stronger neural controls from the upper brainstem or brain are needed to regulate these specialized limbs of humans. In this sense, findings concerning the existence of CPGs are not clearly defined. It can be said that only indirect evidence has been presented for the existence of CPG in humans.

In the human, the body equilibrium is controlled by inputs from proprioreceptors as well as vestibular and visual organs. Mechanoreceptive afferents including proprioreceptive ones are crucial for CPG activity. Particularly, afferents from the load receptors of the hind limbs and those from hip joint position-receptors are the main sources of input to facilitate the CPG activity (Pang and Yang, 2000). Locomotion results from an alternating repetition of stance and swing phases. Extensor muscles are mainly active during the stance phase, whereas flexor muscles act mainly during the swing phase. There is a difference in the control pattern between the flexor and extensor muscles. It is said that the flexors receive stronger cortical projections than the extensors (Brower and Ashby, 1992). Cortical stimulation affects flexors during the distinct swing phase (Schubert et al., 1997). There is a close coordination of muscle activity between the two legs: perturbation of one leg elicits purposeful bilateral responses of the legs. This is performed at the spinal cord level. Even infants can adjust themselves via a cooperative stepping manner on a split–belt treadmill (Thelen et al., 1987).

It is considered that the basic modulator for the stepping remains even in the arm of humans as in the case of quadripedal animals including cats. The responses of arm muscle EMGs are linked with the electrical stimulation of one leg during walking in humans (Dietz et al., 2001). Neural coupling between the arm and leg is considered gated by the regulated activity of the CPG during walking (Cazalets and Bertrand, 2000). Though the CPG in humans has not yet been clearly demonstrated, there have been several studies indicating its existence in humans (Duysens and van de Crommert, 1998).

There is an interesting study that experimentally demonstrated CPG activity in the

human lumbosacral cord (Minassian et al., 2007). Electrical stimulation was applied to the posterior root including the large-diameter afferent fibers that project to motonueurons and interneurons that are involved in motor control of the lower limbs. Interestingly, stimulation at 25–50Hz can elicit rhythmic alternating flexion/extension movements of the lower limbs of SCI patients in the supine position. Similarly, epidural stimulation applied during manually assisted treadmill stepping enhanced stepping-like functional motor outputs in the lower limbs of individuals with complete SCI. These results suggest the existence of a human lumbar locomotor pattern generator, which can convert a tonic input into a rhythmic motor output.

(2) The CPG in patients with SCI

Involuntary rhythmic movements of the trunk and lower limb muscles have been reported in patients with complete spinal cord transection (Kuhn, 1950; Bussel, 1988). This kind of myoclonus activity varied depending on the afferent stimulation, as in spinal animals, and was regarded as generated by the CPG in the spinal cord. The existence of the CPG in humans has also been suggested by some other studies (Dietz et al., 1994; Barbeau and Rossignol, 1994).

The followings are case reports concerning the CPG in patients with SCI.

Calancie et al. (1994) reported the clinical case of 35-year-old male who suffered from an injury to his cervical spinal cord 17 years previously. The subject demonstrated spasticity typical of that seen after chronic spinal cord injury. His ambulation was improved by long-term rehabilitation. During this exercise, he noticed a novel movement: when lying on his back (supine position) and fully extending his hip and knees, stepping-like movement began in his lower extremities and continued as long as he remained supine. The physiological data showed a striking similarity to those described in the spinal cat. Therefore, they concluded that this case demonstrated a well-defined model of a central rhythm generator for stepping in adult humans.

Calancie (2006) also reported 6 rare cases that indicate the existence of CPGs in the human. Patients with complete or incomplete cervical cord injury showed involuntary movements of the trunk and lower limbs.

EMG could be recorded on the trunk and leg muscles to document muscle activation patterns in different postures. The muscle activation patterns were influenced by a variety of sensory stimuli applied to the patients. Involuntary contractions were seen in multiple leg muscles bilaterally. Two patients showed reciprocal movements between agonists and antagonists that alternated between limbs. These movements resembled repetitive stepping.

Pinter and Dimitrijevic (1999) reported that the human lumbar cord isolated from the brain could be trained to respond with rhythmic locomotor-like EMG activity. They found that electrical stimuli applied over the second lumbar segment with a frequency between 2–60 Hz and an amplitude of 5–9 Volts induced rhythmic, alternating stance and swing phases of the lower limbs in a subject with a forced stepping movement using a treadmill.

3. The CPG in rehabilitation

The spinal kitten, in which the spinal cord is isolated from the cerebrum soon becomes able to walk on a treadmill in a fashion similar to that of normal cats. In contrast, the adult spinal cat needs training to improve the effectiveness of hind limb locomotion. This means that CPG plasticity can be modified over time. This phenomenon is called the "rule of spinal cord locomotion"(Pinter and Dimitrijevic, 1999). Even in humans, the CPG might be a major neural circuit that contributes to the generation of rhythmic activity in the isolated lumbosacral spinal cord. Patients with spinal cord injury are trained by partially unloading (up to 60%) on a moving treadmill, basically in the same fashion as spinal cats (Dietz, 1997). Patients are trained to respond with locomotor-like activity to the treadmill movement. Treadmill exercises provide the spinal cord CGP of the patient with manually induced afferent inputs from muscles, tendons, and joints. Load receptive and proprioceptive inputs are vital to drive the CPG in the lumbosacral spinal cord. If patients with complete paraplegia receive treadmill training totally unloaded, no muscle activation is elicited in their legs (Dietz et al., 2002). The afferent inputs from receptors signaling contact forces during the stance phase of the gait are essential for CPG activation. Hip-joint related afferent inputs are also essential to generate a

pattern of locomotion (Dietz et al, 2002). These facts should be taken into consideration for the treadmill-related training of paraplegic patients.

The concept of use-dependent plasticity is important for rehabilitation. Spinal cats can perform stepping more successfully when they are forced to practice this task (Lovery et al., 1990). This fact indicates that neural circuits within the spinal cord can readily be reorganized by practice. It is said that if 10% of the descending pathways are spared, some locomotor function can be recovered by neural reorganization (Basso, 2000). The CPG circuit below the lesion contributes to generate locomotor activity even in the absence of suprapsinal input, in the case of complete transection (De Leon et al., 1998). In addition to the neural network reorganization, neurotansmitters such as noradrenalin, dopamine, and serotonin also contribute to the recovery of locomotion in the spinal cat. Stepping can be induced by the administration of the noradrenegic agonist clonidine (Chau et al., 1998) and serotonin (Schmidt and Jordan, 2000).

Electrical spinal cord stimulation from the epidural space on the posterior side of lumbar spinal cord has become a clinically accepted method for the control of spasticity in SCI patients (Pinter and Dimitrijevic, 1999). In six subjects with complete SCI, nonpatterned electrical stimulation of the posterior structures of the lumbar cord induced patterned locomotor-like activity (Pinter and Dimitrijevic, 1999). Manually controlled stepping, as in the case of treadmill training, generates phasic input, while electrical stimulation of the posterior structures of the lumbosacral spinal cord generate rhythmic locomotor-like EMG activity and stepping movement.

As stated above, leg loading is important for patient with paraplegia to generate the stepping movement by training. Fully unloaded training cannot generate leg muscle activation for the stepping movement. Spinal reflexes such as the stretch reflex constitute only a minor contribution to the recovery of stepping movement. Load receptors and hip joint position-afferents are critical factors to stimulate the CGP to induce locomotion. The CPS is quite flexible after injury. Rehabilitation should utilize this neural plasticity.

In his review, van der Crommet et al. (1998)

stated that improved function of locomotion is seen in SCI patients with either an incomplete or complete lesion, when trained on a treadmill with body weight support. The most important features are an improved modulation pattern of EMG activity in muscles of the lower limbs and an increased ability to support the body weight. This suggests that the CPG can be activated in paraplegic patients in a manner similar to the chronic spinal treadmill-trained cat. Complete SCI patients never exhibit unassisted stepping. The inability of completely paralyzed subjects to achieve unassisted mechanical stepping suggests that the level of human dependence on supraspinal and/or proprioceptive inputs to generate stepping differs at least quantitatively from that of quadrupedal mammals.

Calasie (2006) reported six patients with SCI (4 complete and 2 incomplete SCI) who demonstrated involuntary myoclonus. This movement depends on posture. The timing, distribution and dependency on the hip angle suggest that these movement patterns reflect some elements of a CPG. The rate of such patients is very low, about 1%.

Dietz et al. (1994) studied five patients with complete and 4 with incomplete SCI. The patients were subjected to training on a moving treadmill and body weight support via parachute harness connected to a winch (Fig. 1). The pattern of muscle EMG activity was similar to that seen in healthy subjects although the EMG amplitude was smaller. With daily training, the amplitude of gastrocnemius EMG activity increased during the stance phase of stepping, and the degree of inappropriate tibialis anterior activity decreased during this phase (Fig. 2). The walking of patients with incomplete paraplegia improved following the training programs.

Wernig et al. (1995) described 89 patients with incomplete SCI who undertook treadmill therapy. The program consisted of daily upright walking on a motor-driven treadmill initially with body support provided by a harness and limb movements assisted by therapists when necessary. They had been injured 0.5–18 years before this treatment. The therapy continued for 3–20 weeks. Out of 33 wheelchair-bound chronic patients, 25 learned to walk independently, and 7 patients could walk with help at the end of the therapy. Only one patient did not improve.
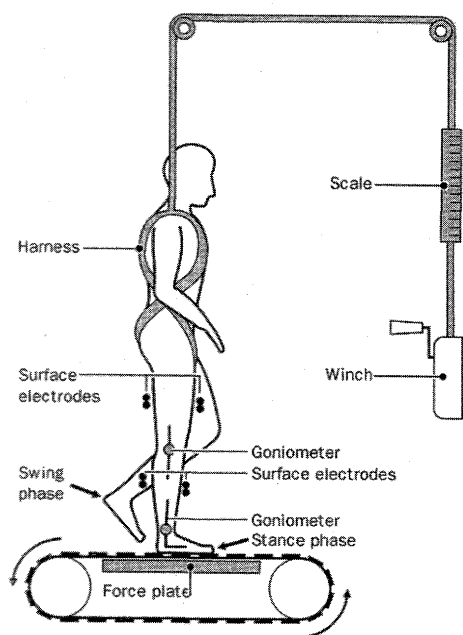
Figure 1   This drawing shows the experimental set-up for stepping movement. Patients with complete or incomplete paraplegia were supported with a harness, and the stepping movement is induced by treadmill.   Electromyographic (EMG) recordings were made from the surface electrodes on the gastrocnemius and tibialis anterior muscles of both legs.   Ankle and knee joint movements were measured by goniometers fixed on the lateral aspects of the ankles and knees. A force plate recorded the force exerted by the legs on the treadmill. Each step cycle was adjusted to a relative time scale of a step-cycle starting and ending with the right heel strike.
(Reproduced from Lancet 344, Dietz et al. Locomotor activity in spinal man, pp1260–1263, 1994, with permission from Elsevier)
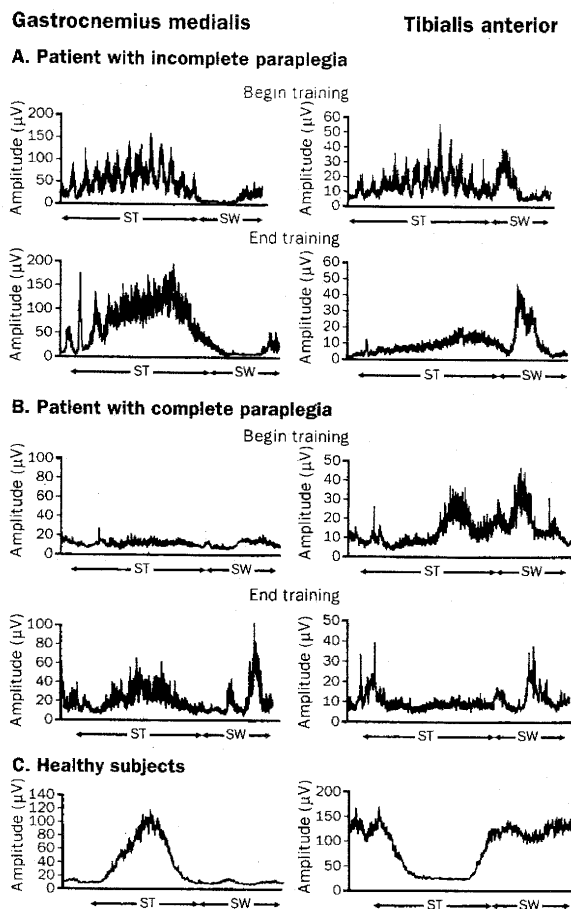

Figure 2   These graphs show rectified and averaged EMG activity of lower-leg muscles during locomotion (around 1.3km/h) of 1 patient each with incomplete (A) and complete (B) paraplegia, and group average of five healthy subjects (C).   The amount of support for healthy subjects was 50% of body weight; patient A at the start of training, 30kg and end, 0kg of 82kg, patient B at the start of training, 50kg and end, 35kg of 67kg.
St=stance, and SW=swing phase.
(Reproduced from Lancet 344, Dietz et al. Locomotor activity in spinal man, pp1260–1263, 1994, with permission from Elsevier)

In summary, an appropriate afferent stimulation is vital to drive the CPG. In addition, the intrathecal delivery of drugs including noradrenalin, DOPA, and serotonin is effective to generate alternating rhythmic movements in the CPG. Treadmill training can provide subjects with a partial load of body weight, which can elicit phase-dependent afferent inputs during stance and swing phases. These load-receptive afferent inputs are important to drive CPG activity.

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