Because SCI triggers complicated biological processes and also leads to a variety of neuronal deficits, the use of several approaches should be considered. The approaches can be categorized into the "hardware" and "software" approach. "Hardware" implies the neural network through which all neural activities take place. Just as a computer does not work unless a suitable program is installed, the neural "hardware" also requires neural programs that control limbs and coordinate movement. In the neural network, such programs include proper synaptic connections, which facilitate basic voluntary movement of the limbs and learning of complex motor patterns. Traumatic disturbance in the neural circuit leads to the simultaneous reorganization and reprogramming of the neural circuit. With regard to therapeutic intervention, the "hardware" approach would entail pharmacological therapy for neuroprotection in patients with acute phase SCI or it would entail tissue engineering for the restoration of the neural structure. On the other hand, rehabilitation and training, which facilitate use-dependent plasticity, are regarded as "software" approaches (Fig. 1).

The molecular and electrophysiological approaches both can be used for analysis of nervous system disorders and therapeutic intervention. The molecular approach is based on the knowledge of molecular cellular biology and aiming to modulate cellular functions in patients with SCI. For example, cell death modulation and apoptosis are closely related to the prevention of secondary injury, which is reported to be a main cause of progressive damage in patients with acute phase SCI. In the same manner, basic research on axonal elongation revealed the existence of inhibitory factors

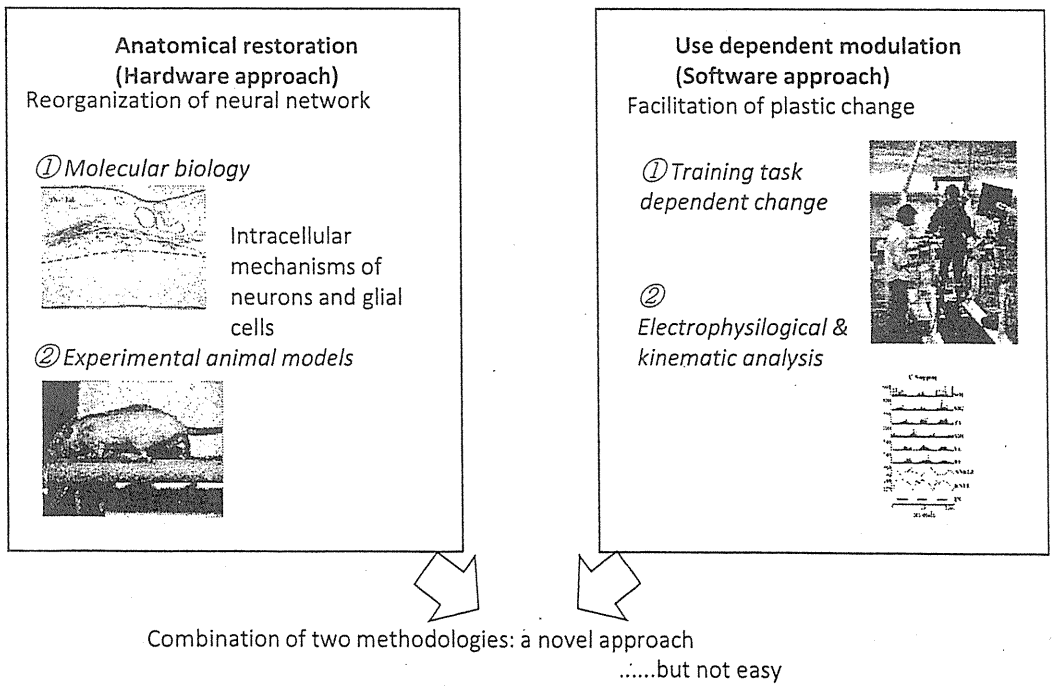

Fig. 1 Two methodologies for intervention in spinal cord injury. There are molecular approaches (*left*) and electrophysiological approaches (*right*) for analyzing and biological processes after SCI and providing therapeutic intervention

such as Nogo in the injured spinal cord, which acts on a group of receptors that induce the growth cone shrinkage leading to the termination of axonal regeneration. Now, this molecular mechanism is regarded as a therapeutic target to induce axonal regeneration, and various pharmacological approaches based on this are now in the preclinical stages of investigation. Taken together, the molecular approach is thought to be an effective means of modifying the neural structure (hardware).

On the other hand, the electrophysiological approach is effective in measuring or modulating neural functions. Various noninvasive means such as electromyography, measurement of nerve conduction velocity, and transcranial magnetic stimulation are used to assess the connectivity of supraspinal circuits and distal neural circuits, and the excitabilities of the corticospinal tract in human subjects. Recently, it is also used as a method to modify neural activities in the central nervous system through the use of transcranial magnetic stimulation or transcranial direct current stimulation. Therefore, these methods are effective in detecting or inducing plastic change in neural activities, which is related to "software."

To establish a multidisciplinary approach to SCI, it would be interesting to combine those approaches, so that the basic knowledge of molecular biology can be applied directly to a clinical setting. However, there have not been many models that have been used successfully for this purpose probably because of the unavailability of a proper animal spinal cord injury model for observing plastic change in neural activity in an electrophysiological manner. Therefore, at this point, it would be better to utilize either of the two methodologies depending on the clinical problem that needs to be solved.

Approaches for Treating Complete Spinal Cord Injury

Patients with SCI show varied symptoms and levels of severity. With regard to severity, there is (1) complete SCI, i.e., complete loss of sensory and motor functions below the lesion, and there is also (2) incomplete SCI, i.e., preservation of sensory and motor functions. In the case of complete SCI, especially in patients with severe dislocation of the spinal column, the connection between the brain and lower circuits seems to be completely lost. In such cases, it is important to restore some connection beyond the lesion before considering reprogramming the reorganized neural circuits. For this purpose, the molecular approach has an advantage over the electrophysiological approach.

As mentioned above, molecular biology has revealed much about the mechanisms governing axonal elongation. Especially, the intracellular mechanisms that are triggered by nerve growth factor stimuli have been investigated in detail. Nerve growth factors (NGFs), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) bind to their own receptors expressed on the cell surface of neurons and transduce their effects via phosphorylation cascades of signaling molecules within the cell, which finally induce gene expression for axonal elongation. Among several signaling cascades, activation of the Mek–Erk signals is said to be important,

and it has been shown that Mek activation is sufficient to induce axonal growth in PC12 cell line – a model cell line for neurite growth – even in the absence of nerve growth factors. Miura et al. examined the application of this paradigm in a spinal cord injury model [1]. In their report, he transected rat spinal cord at the thoracic 10 level and injected an adenovirus gene transfer vector into the parenchyma of the proximal stump. This type of gene transfer delivered the gene to not only the segmental neural cells in the spinal cord but also the primary motor neurons in the brain, such as the red nucleus, by retrograde transport along the axons. After 6 weeks of spinal transection and simultaneous gene transfer of the control gene (LacZ) or the constitutively active *Mek* gene, the effect of gene transfer was examined by both behavioral and histological evaluation. Behavioral evaluation using the Basso, Beattie, and Bresnahan (BBB) scale [2], which has been a well-accepted hind limb motor scoring scale in a rat spinal cord injury model, showed better functional recovery in the active Mek-transferred group than in the control group (Fig. 2). Histological evaluation performed by injecting an anterograde neuronal-tracer into the red nucleus

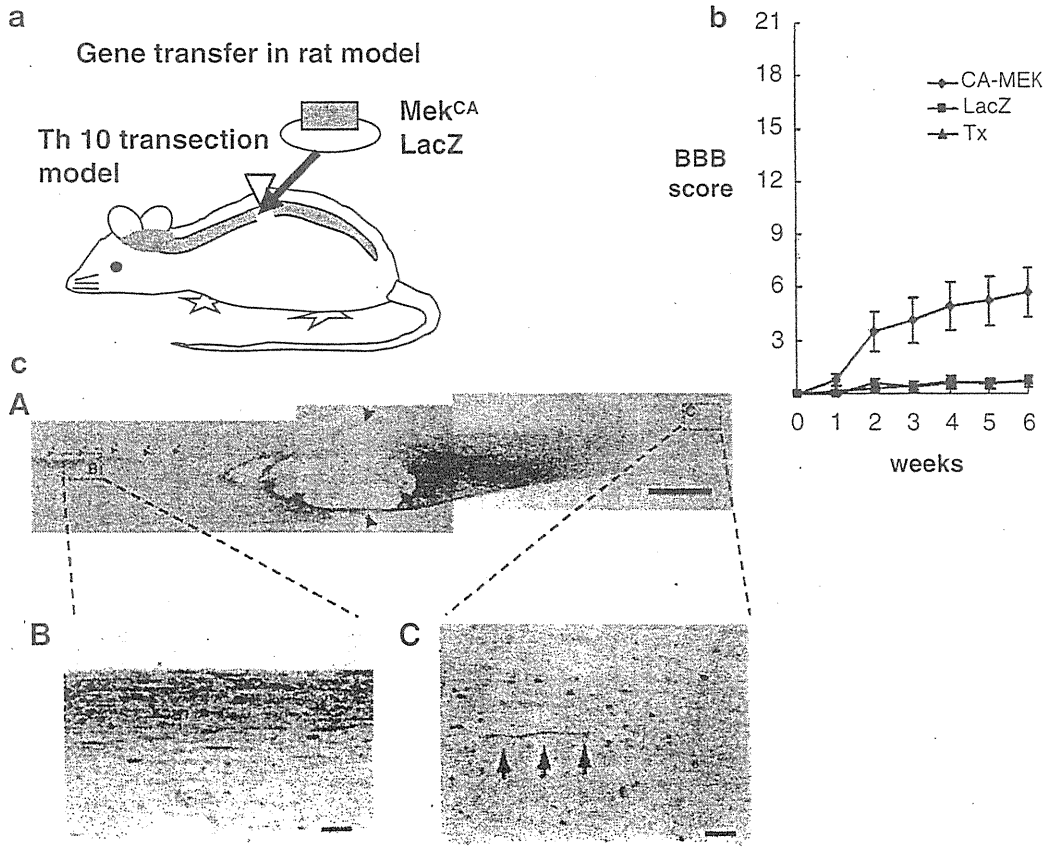

Fig. 2 A molecular approach for treating complete SCI. For complete SCI, we have shown the restoration of axonal connectivity between the supra-spinal circuit and the area below the lesion. (**a**) Schematic image of the transfer of a gene to the transected spinal cord using adenoviral vectors. (**b**) Functional recovery was observed in the CA-MEK transferred group, in which the intracellular MEK–ERK signaling cascade is constitutively activated in primary motor neurons of the brain. (**c**) Histological examination reveals axonal regeneration beyond the lesion (anterograde neurotracing)

showed marked regeneration of the rubrospinal tract beyond the complete transection site. Taken together, activation of intracellular signals within the primary motor neuron in the brain can be one of the approaches to retain functional recovery in cases in which the axonal connection is completely lost at the lesion site.

Approaches for Treating Incomplete Spinal Cord Injury

The therapeutic strategy for patients with incomplete SCI should be different from that for those with complete SCI. Because the symptoms for this condition are varied and the degree of severity and the segment injured varies among patients with incomplete SCI, the patient's condition needs to be thoroughly investigated, and the aspect of neural function that requires treatment should be determined. For example, the treatment approach for a patient who cannot stand even with support should differ from that for one who can walk with support but with a spastic gait. Here, we will discuss gait rehabilitation in patients with incomplete SCI, especially those who can stand with assistive tools and walk a few steps with assistance. These patients are classified as Frankel C and are considered to probably have SCI of "mild" severity. However, it is not practical for these patients to perform locomotion activity.

With regard to the modification of neural functions, physiological functions should be strengthened; and abnormal functions, corrected. Besides facilitation of voluntary movement of the lower limbs, automated movement of limbs is also considered an important physiological neural function in those patients. While walking, individuals do not have to pay attention to how to move their hip, knee, and ankle joints. It has been shown that a certain "gait program" exists within the central nervous systems and that we utilize this program. The existence of the gait program is shown using an experimental model of decerebrate cats [3–5] and also human subjects [6–8] on a treadmill; it revealed that the program is located in the spinal cord, and this program is now called the "central pattern generator (CPG)." We also examined the functions of CPG in patients with SCI under our experimental settings. By using the training device Easy Gait Glider (Altimate Medical Inc., USA), we produced passive lower limb motion in an alternating manner and recorded electromyographic (EMG) signals in the lower limbs. Figure 3b shows the activities of each muscle that is completely paralyzed in the subject. Because we observed rhythmic burst from the right and left legs as observed when the limbs make stepping movements, we assumed that the CPG in this subject was activated. With the same device, we can also investigate which components of passive leg motion are critical for CPG activation. If the observed EMG activities are induced by stretch reflex in each leg, the same EMG activities are expected when only one leg is passively moved or both legs are passively moved but in a synchronized manner and not in an alternating manner. Even though the kinematic parameters of the examined leg were exactly the same under the experimental conditions, we only observed a gait-like EMG pattern in those patients who showed passive leg motion in an alternating

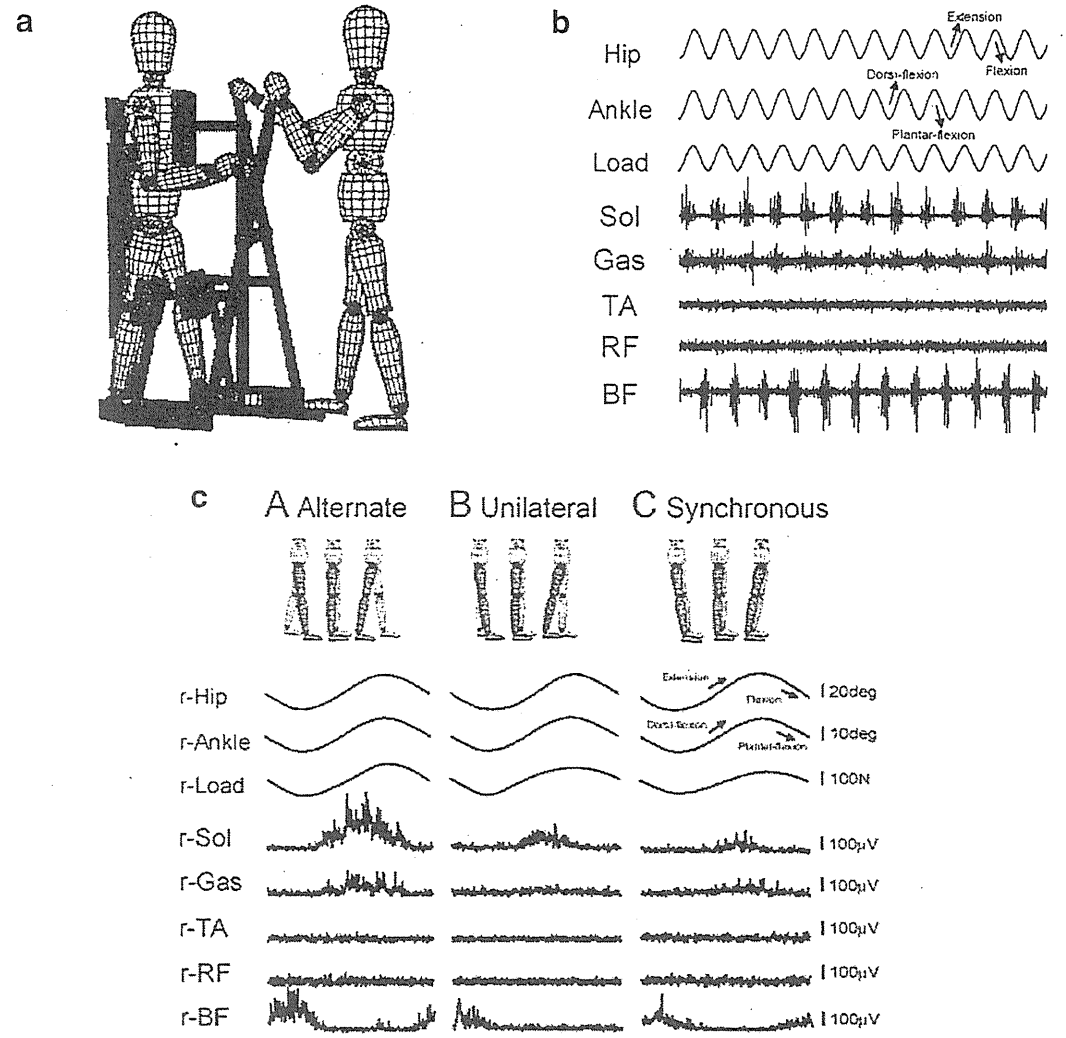

Fig. 3 An electrophysiological approach to incomplete SCI. For patients with incomplete SCI, we have shown that the activation of the central pattern generator is one of the key elements for the restoration of locomotive function. (**a**) Passive leg exercise using the Easy Stand Glider. (**b**) Phasic EMG activities in the soleus (Sol), gastrocnemius (Gas), and biceps femoris (BF) muscles during passive leg exercise in patients with complete SCI. (**c**) Alternate leg motion is necessary for the induction of gait-like EMG activities. Even though kinematic parameters are equivalent, EMG activities evoked during alternate passive leg motion are much stronger than those evoked during unilateral or synchronous leg motion

manner (Fig. 3c). These results indicate that CPG activation is specific to afferent stimuli resulting from alternate leg motion [9].

The existence of spinal CPG in individuals with and without SCI gives an idea of the kind of strategy required for rehabilitation of patients with incomplete SCI. Because CPG activation plays a pivotal role in locomotion, optimization of CPG activities will improve locomotive functions for those classified as Frankel C. In a more systematic manner, we envision a possible three-step approach, including (1) application of correct afferent input, (2) utilization of intersegmental coordination (this refers to a combination of the leg and arm swing), and (3) production of a

descending command from the cortex. To develop an optimized CPG activation training protocol, electrophysiology is one of noninvasive approaches for evaluating the activities of CPG. For example, the second component of the above scheme, i.e., inter-segmental coordination, can be tested using the Easy Stand Glider. Kawashima et al. performed experiments in which patients with SCI were placed in the Easy Stand Glider while their arms were resting or were in passive or active swing, and alternative passive motion was applied to the lower limbs with the same kinematics [10]. In this experiment, they observed that along with arm swing, the subjects showed more gait-like EMG activation in their lower limbs. Interestingly, abnormal EMG activity, such as unfavorable contraction of the soleus muscle during swing phase, was reduced in some subjects when they were made to perform arm swing as well. Taken together, they concluded that the arm swing will facilitate CPG activation both by both promoting physiological EMG pattern and reducing abnormal EMG pattern.

Because passive gait training induces CPG activation as described above, it is reasonable to apply these principles for the rehabilitation of patients with incomplete SCI. For such a purpose, the recently developed training device Lokomat (Hocoma, Zurich, Switzerland) is useful. Lokomat is an exoskeleton gait assistive device, which controls the hip and knee joints of subjects on body weight-supported treadmill [11]. The concept is based on assistive gait training provided by a physiotherapist. Taking advantage of automated assistance and robotic machinery, Lokomat can provide reproducible gait kinematics with a few non-physiotherapists. Because Lokomat provides physiologically oriented gait-like kinematics to subjects, passive gait training using Lokomat is expected to induce CPG activation in the same manner, or even in a more efficient manner, as observed when using the Easy Stand Glider. Further investigation studies should focus on whether the activation of CPG during training sessions has any long-lasting effects on the locomotive function of subjects.

A Novel Approach for Evaluating Prognosis of Patients with SCI

Some novel approaches for patients with complete and incomplete SCI, including the abovementioned Lokomat training method, are being tested in the preclinical stage. For the application of these therapies, the methods of evaluating the spinal condition are also very important. In particular, it should be noted that spontaneous recovery has been observed in patients with SCI in Frankel B–C. It has been reported that on admission, patients who presented with SCI of Frankel B to C showed significant spontaneous recovery within several months to a year [12]. Therefore, it is hard to determine the efficacy of any therapeutic intervention on the basis of the functional recovery in each patient. Thus far, a neurological examination is the only means of assessing the severity of the injury; however, alternative methods of evaluating the severity of the condition are required.

For diagnosing central nervous system disorders, the use of blood and cerebrospinal fluid (CSF) samples and the measurement of specific protein levels

have also been attempted. The proteins are regarded as biomarkers as they help monitor the disorder. For example, the intracellular calcium binding protein S100B has been a candidate biomarker for patients with subarachnoid hemorrhage [13]. Because the glial cells in the brain are enriched with the S100B protein, S100B is thought to be released in the blood upon damage to the cells, which leads to its increased expression in the blood. As for patients with SCI, there are not many reports on useful biomarkers for this condition. Kwon et al. measured CSF levels in 30 patients with SCI and found a certain correlation with functional severity [14]. However, it is not always feasible to obtain CSF samples from patients with acute phase SCI; therefore, it is preferable to obtain information from blood samples.

Recently, Shaw et al. reported that a certain type of neurofilament, i.e., the phosphorylated form of a high-molecular-weight neurofilament subunit NF-H (pNF-H) [15], is released into the blood after damage of the central nervous tissue and is more stable compared to conventional biomarker candidates. Therefore, the elevated concentration of pNF-H in the blood is thought to reflect axonal damage of the neural tissue. In contrast to the other biomarkers of neural injury, pNF-H can be detected after 24 h in experimental spinal cord contusion injury in rodents and peaks 3–4 days later, whereas most other biomarkers peak within 24 h. The time point at which the pNF-H level best reflects the initial severity of the trauma remains unknown. Further, pNF-H can be a useful tool for evaluating the efficacy of pharmacological intervention in patients with acute SCI because pNF-H can be detected in the blood for several days and may reflect progression of secondary injury to axons. In our recent work, we examined the pNF-H concentration in SCI rats treated with either intraperitoneal administration of minocycline or saline (control). Minocycline is known to be a neuroprotective drug and several reports have revealed its efficacy in functional recovery in an animal SCI model [16]. Under our experimental conditions, we also confirmed the effectiveness of minocycline using the end-point functional motor score of the hind limb of rats (28 days after injury) (Fig. 4b). At the same time, the level of pNF-H in the plasma shows a difference 3–4 days after injury (Fig. 4a). The minocycline-treated group tended to have a lower pNF-H level, which was in accordance with their improved motor recovery. Taken together, the pNF-H level can be used not only as a diagnostic tool for the initial severity of SCI but also as a monitoring tool after therapeutic intervention. It still needs to be investigated whether pNF-H is measurable in patients with SCI and whether it can serve as a biomarker.

Conclusion

We have discussed the possibilities of the use of the electrophysiological and molecular approaches for SCI treatment. Although a direct combination of the two paradigms is not feasible at the moment, we can select either method depending on the clinical problem that needs to be solved. Generally, the molecular approach is useful when attempting to restore or preserve neural tissue structure, i.e., the hardware of the spinal cord, whereas the electrophysiological approach can be used for modulating

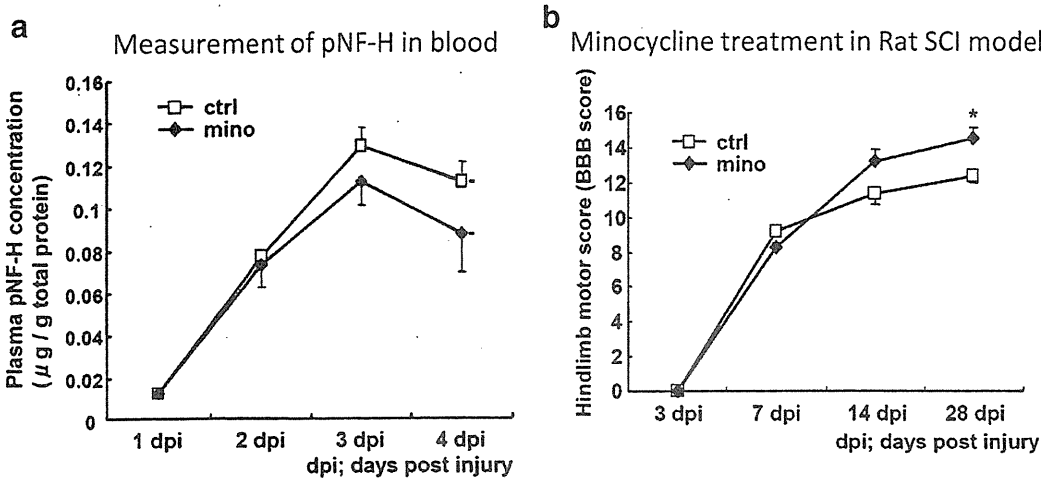

Fig. 4 A molecular approach for evaluating the severity of SCI. The phosphorylated form of high-molecular-weight neurofilament subunit NF-H (pNF-H) is a novel biomarker of central nervous system disorders. (a) The plasma pNF-H concentration was compared between minocycline-treated and saline-treated groups in SCI induced in rats. The reduction in the pNF-H level at 3 and 4 days after the injury in minocycline-treated groups indicate less axonal damage in this group. (b) The reduction in the plasma pNF-H level coincides better with functional recovery in the hind limb

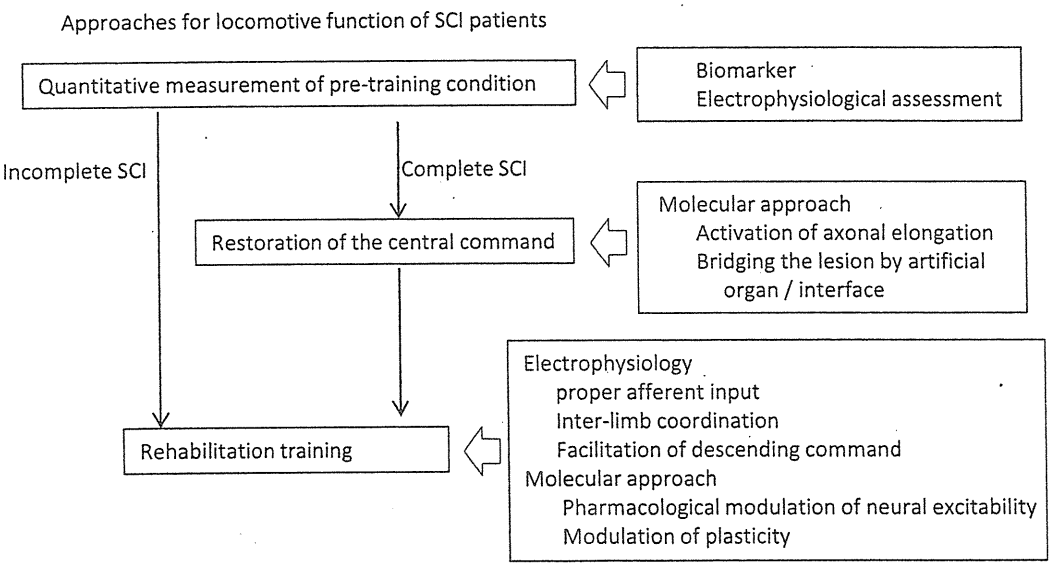

Fig. 5 A frame format of approaches for spinal cord injury. Even though a combination of the molecular and electrophysiological methods is difficult, we can use either methodology, depending on the clinical problem that needs to be solved

or evaluating use-dependent plasticity, or in other words the software of spinal neural circuits. To solve various clinical problems in SCI, the first step is to clarify the therapeutic target in each case. Further, we should prepare proper evaluation systems on the basis of the therapeutic targets, in which we can use both electrophysiological and molecular approaches (Fig. 5).

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Robotic-assisted stepping modulates monosynaptic reflexes in forearm muscles in the human

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[1]Motor Control Section, Department of Rehabilitation for the Movement Functions, Research Institute, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan; [2]Rehabilitation Neuroscience Laboratory, University of Victoria, British Columbia, Canada; [3]Graduate School of Engineering, Shibaura Institute of Technology, Tokyo; [4]Graduate School of Systems and Information Engineering, University of Tsukuba, Ibaraki; and [5]Division of Health and Sports Sciences, Faculty of Education, Chiba University, Japan; [6]Motion and Mobility Laboratory, University of Victoria, British Columbia, Canada; and [7]Graduate School of Arts and Sciences, University of Tokyo, Japan

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Nakajima T, Kitamura T, Kamibayashi K, Komiyama T, Zehr EP, Hundza SR, Nakazawa K. Robotic-assisted stepping modulates monosynaptic reflexes in forearm muscles in the human. *J Neurophysiol* 106: 1679–1687, 2011. First published July 20, 2011; doi:10.1152/jn.01049.2010.—Although the amplitude of the Hoffmann (H)-reflex in the forelimb muscles is known to be suppressed during rhythmic leg movement, it is unknown which factor plays a more important role in generating this suppression—movement-related afferent feedback or feedback related to body loading. To specifically explore the movement- and load-related afferent feedback, we investigated the modulation of the H-reflex in the *flexor carpi radialis* (FCR) muscle during robotic-assisted passive leg stepping. Passive stepping and standing were performed using a robotic gait-trainer system (Lokomat). The H-reflex in the FCR, elicited by electrical stimulation to the median nerve, was recorded at 10 different phases of the stepping cycle, as well as during quiet standing. We confirmed that the magnitude of the FCR H-reflex was suppressed significantly during passive stepping compared with during standing. The suppressive effect on the FCR H-reflex amplitude was seen at all phases of stepping, irrespective of whether the stepping was conducted with body weight loaded or unloaded. These results suggest that movement-related afferent feedback, rather than load-related afferent feedback, plays an important role in suppressing the FCR H-reflex amplitude.

flexor carpi radialis; Hoffmann reflex; *soleus* muscle; passive stepping; stepping-related feedback

DURING RHYTHMIC ARM CYCLING, Hoffmann (H)-reflex amplitude in the *soleus* muscle (Sol) is strongly suppressed in humans (Frigon et al. 2004; Hundza and Zehr 2009; Loadman and Zehr 2007). Interestingly, leg cycling also leads to suppression of the H-reflex amplitude in the forearm muscles (Zehr et al. 2007). These results suggest a reciprocally organized pattern-generating system activated by descending locomotor commands and afferent feedback that modulates reflex excitability in remote muscles (Zehr and Duysens 2004; Zehr et al. 2009). Currently, though, the neural mechanisms producing this organization remain unclear.

Loadman and Zehr (2007) suggested that central commands for rhythmic arm cycling were a major source of modulation, because differences in the range of arm motion (i.e., range of muscle-length change) did not alter H-reflex amplitude in stationary leg muscles. A central source for the modulation is also suggested by the observation that active arm cycling induces phase-dependent modulation of the Sol H-reflex (de Ruiter et al. 2010). In addition, Hundza et al. (2008) suggested that suppression of the Sol H-reflex during passive arm cycling was small compared with during active arm cycling. These reports suggest that central drive for rhythmic arm movement is important in suppressing H-reflexes in the ankle extensor muscles. Considerably less is known about the modulation of H-reflexes in arm muscles during passive leg movement, and the underlying mechanisms require further clarification. Importantly, the extent to which modulation of reflex excitability within a limb muscle can be fully accounted for by central drive or different sources of afferent feedback is unclear. Answering this means determining the relative contributions of movement-related afferent feedback, load-related bias, and central motor commands in the amplitude modulation of H-reflexes in forearm muscles.

Phase-dependent modulation of H-reflex amplitude in arm muscles during rhythmic leg movement remains an uncertain area. Phasic modulation of the forearm flexor H-reflex was seen with isolated, rhythmic foot movement (Baldissera et al. 1998) but not with rhythmic leg cycling (Zehr et al. 2007). Currently, there are no comparable data from arm muscles during walking-based driven gait orthosis (DGO) stepping and passive movement of the leg. Since passive DGO leg movement resembles "passive" cycling as a whole-leg rhythmic locomotor movement, we hypothesized that the passive stepping would suppress H-reflex amplitudes in the forearm, irrespective of body loading and without phase-dependent modulation.

We demonstrated previously that phase-dependent, cutaneous reflex modulation was absent in leg muscles during unloaded stepping, during passive stepping, suggesting that load-related afferents were important for generating phasic modulation of the cutaneous reflex in leg muscles (Nakajima et al. 2008). However, a similar approach did not affect Sol H-reflex modulation, suggesting that the effect of loading during passive stepping strongly depends on excitability in reflex circuitry (Kamibayashi et al. 2010). This parallels the earlier suggestion of Zehr et al. (2001), showing a differential mod-

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ulation of cutaneous and H-reflexes in leg muscles depending on motor output and loading during leg cycling. However, it is not known whether lumbar load-related afferent feedback modulates the excitability of monosynaptic H-reflex circuits in the cervical spinal cord. We hypothesized that although we can expect a modulation in H-reflex amplitude in the remote limb, loading should have only a small effect on phase-modulation during DGO passive stepping. Absence of a modulatory effect of load-related afferent feedback on H-reflex excitability would implicate movement-related afferents in contributing to the pattern of H-reflex modulation observed during passive leg movement.

MATERIALS AND METHODS

Subjects

Participants were 16 healthy males, aged 22–32 yrs. All gave informed, written consent prior to participation in the experiments. The protocol was approved by the local ethics committee of the National Rehabilitation Center for Persons with Disabilities (Saitama, Japan) and is in accordance with the guidelines set out in the Declaration of Helsinki (1964).

General Procedure

The recently developed DGO system, Lokomat (Hocoma AG, Volketswil, Switzerland), was used to produce "passive stepping", defined as stepping movements driven by the DGO system while relaxing the leg muscles. In this paradigm, there may be some very low-level, incidental muscle activation, but it is involuntary (see Kamibayashi et al. 2009). A detailed description of the Lokomat can be found elsewhere (Colombo et al. 2001). Briefly, this system consists of a treadmill, a body-weight support system, and two robotic actuators that are attached to each subject's legs. The Lokomat is fully programmable, including the control of knee and hip kinematic trajectories during different types of stepping, with and without body-weight loading.

The right forearm, wrist, and hand were fixed to a rigid platform to minimize any unwanted movement of the arm. A brace was worn to restrict arm movement and was fixed on the elbow and wrist positions at 90° and 0°, respectively, in all experiments. All trials were performed when the *flexor carpi radialis* (FCR) muscle was quiescent. Unloading of body weight was accomplished by suspending the subject's body with a harness connected to an overhead crane. For all passive stepping conditions, the treadmill speed was kept constant at 2.0 km/h for all subjects. During passive stepping, the subjects were instructed to relax and allow the lower-limb movements to be imposed by the DGO. Dorsiflexion of the ankle joint during the stepping condition was achieved by passive foot lifters (spring-assisted elastic straps) to prevent foot drop at the swing phase (see Kamibayashi et al. 2010).

Experimental Tasks

To explore the effect of passive leg stepping on the upper arm H-reflex amplitude, subjects participated in three experiments using the Lokomat systems: *1*) phase-modulation of the FCR H-reflex during passive stepping ($n = 10$); *2*) determination of the H-reflex and muscle response (M-wave; H-M) recruitment curves during passive stepping ($n = 8$; all participated in *experiment 1*); and *3*) effects of loading on the FCR H-reflex during passive stepping ($n = 10$). Of these last 10, four participated in one or both of the other experiments, and six participated only in this experiment. When a given subject participated in two or three experiments, data from each experiment were collected on different days. Based on a previous study (Javan and Zehr 2008), the intervening time interval is sufficient for residual suppression to disappear; thus our results across experiments were not affected by residual suppression. During experiments to investigate phase-modulation and the effect of loading on FCR H-reflex amplitudes, experimental conditions (phases or load conditions) were pseudo-randomly executed for each subject.

Effect of stepping-related afferent feedback on FCR H-reflex. In 10 subjects, the effect of leg stepping-related afferent feedback on the FCR H-reflex amplitude was investigated during robotic-assisted passive stepping and standing conditions (40% unloading of body weight). The subjects performed passive stepping on the treadmill with the arms at rest. Electrical stimulations to elicit the H-reflex were pseudo-randomly delivered at 10 different phases of the stepping tasks (see *FCR H-reflexes* below).

Effect of load-related afferent feedback on FCR H-reflex during DGO stepping. To investigate the effect of load-related afferent feedback on the FCR H-reflex during passive stepping, 10 subjects performed passive stepping and standing in separate trials under two conditions: *1*) unloaded condition (100% of body-weight support) above the treadmill belt and *2*) loaded condition (40% unloading of body weight) on the treadmill (Kamibayashi et al. 2009, 2010). Reflexes were evoked at the midstance phase and during standing, with and without loading of body weight for all trials.

FCR H-Reflexes

FCR H-reflexes in the right arm were evoked by stimulating (rectangular pulse, 0.5-ms duration) the median nerve with a constant current electrical stimulator (SEN-7023, Nihon Kohden, Tokyo, Japan). Bipolar stimulus electrodes were placed just proximal to the medial epicondyle of the humerus, near the *cubital fossa* (cf. Zehr et al. 2007). To examine the effect of leg position on FCR H-reflex in the passive stepping, the step-cycle duration was set at ~2.0 s by the Lokomat system and divided into 10 phases. The step duration was chosen to ensure subjects' safety and effectively avoid unintentional electromyographic (EMG) activity of the leg muscles. The electrical stimulations were pseudo-randomly delivered at various times during the stepping tasks (0, 200, 400, 600, 800, 1,000, 1,200, 1,400, 1,600, and 1,800 ms after the trigger signal), defined by predetermined hip-joint angles. The trigger signal was made by hip angles coincident with the timing of heel contact. These stimuli were delivered randomly once every two to three step cycles. The stimulus intensity was adjusted to ~10% of the maximal amplitude of the direct motor response (M_{max}) in each phase (cf. Kamibayashi et al. 2010; Simonsen and Dyhre-Poulsen 1999). These stimulation intensities were confined to H-reflex amplitudes evoked on the ascending limb of the recruitment curve of the H-reflex. The consistency of the test stimulus was confirmed by examining the shape and peak-to-peak amplitude of the M-wave. As controls, M_{max} ($n = 5$ sweeps) and H-reflex ($n = 12$ sweeps) amplitudes were measured during standing and at each of the 10 stepping phases.

In additional control experiments, the H-M recruitment curves were recorded in eight subjects during quiet standing and at the stance and swing phases of passive stepping. The stimulus intensity was increased gradually from below the threshold of the H-reflex to supramaximum stimulation of the M-wave. Five responses were recorded at each of the stimulus intensities.

To investigate the effect of load-related afferent feedback on the FCR H-reflex amplitude during passive stepping, recruitment curves were also recorded during standing and at the stance phase of passive stepping, with and without loading of body weight in 10 subjects. All trials were performed when FCR was quiescent.

EMG Recording

EMG activity was recorded from the FCR, *extensor carpi radialis* (ECR), *rectus femoris* (RF), *biceps femoris* (BF), *tibialis anterior*

(TA), and Sol muscles on the right side. EMG signals were obtained with surface electrodes (SS-2096, Nihon Kohden) over the belly of each muscle after reducing skin impedance (below 10 kΩ) by light abrasion and alcohol cleaning. All EMG signals were amplified (×1,000) and band-pass filtered between 15 Hz and 3 kHz via a bioamplifier system (MEG-6108, Nihon Kohden). All EMG and angular signals were converted to digital data with an analog-to-digital converter card [Micro1401, Cambridge Electronic Design (CED), Cambridge, UK] and stored on a hard disk with a sampling rate of 5 kHz using Spike2 software (CED).

Data Analysis

Peak-to-peak amplitudes of M-waves and H-reflexes were normalized to the respective M_{max} amplitudes recorded during standing and at each phase of stepping.

Analysis of H-M recruitment curve. H-reflex amplitudes from the standing control curves were compared with those from the same values induced by electrical stimulation on the curves conditioned by stepping at midswing and midstance (Klimsta and Zehr 2008; Mezzarane et al. 2011; Zehr et al. 2007). Stimulus intensities for eliciting the maximum H-reflex (H_{max}) and ~50% H_{max} values were defined from the recruitment curves obtained during the standing control. For the H-M recruitment curve, means and SDs were calculated and plotted with respect to the intensity of electrical stimulation (recruitment curve; see Figs. 5 and 7).

Reflex amplitudes of the standing, midswing, and midstance phases of stepping, obtained by two stimulus strengths for eliciting ~100% and ~50% of the H_{max} at control, were compared using two-way repeated measures (RM) ANOVA (three conditions × two stimulus intensities). Two-way RM ANOVA was also used to examine modulation of the H-reflex amplitudes, with and without loading at the stance phase of passive stepping and during standing (two load conditions × two tasks).

Analysis of the FCR H-reflex amplitude at the 10 stepping phases and during standing. The H-reflex, M-wave in the FCR and background (BG) EMG activities in the FCR, ECR, RF, BF, Sol, and TA were compared using a one-way RM ANOVA [factors; standing control and passive stepping (10 phases of step cycle)]. The BG EMG activity was calculated as the root mean square value of the EMG signal for 50 ms before the electrical stimulation. Multiple comparisons were performed using the Bonferroni post hoc test. The data were expressed as means ± SEM. Significant differences were recognized at $P < 0.05$ in all cases. All statistical tests were performed using SPSS software version 11.0 (SPSS, Chicago, IL). The F values and degrees of freedom were obtained after Greenhouse-Geisser correction when appropriate.

RESULTS

EMG and Kinematic Patterns during Passive Stepping

Figure 1 shows typical recordings of EMG activities and joint angles during passive stepping (40% unloading of body

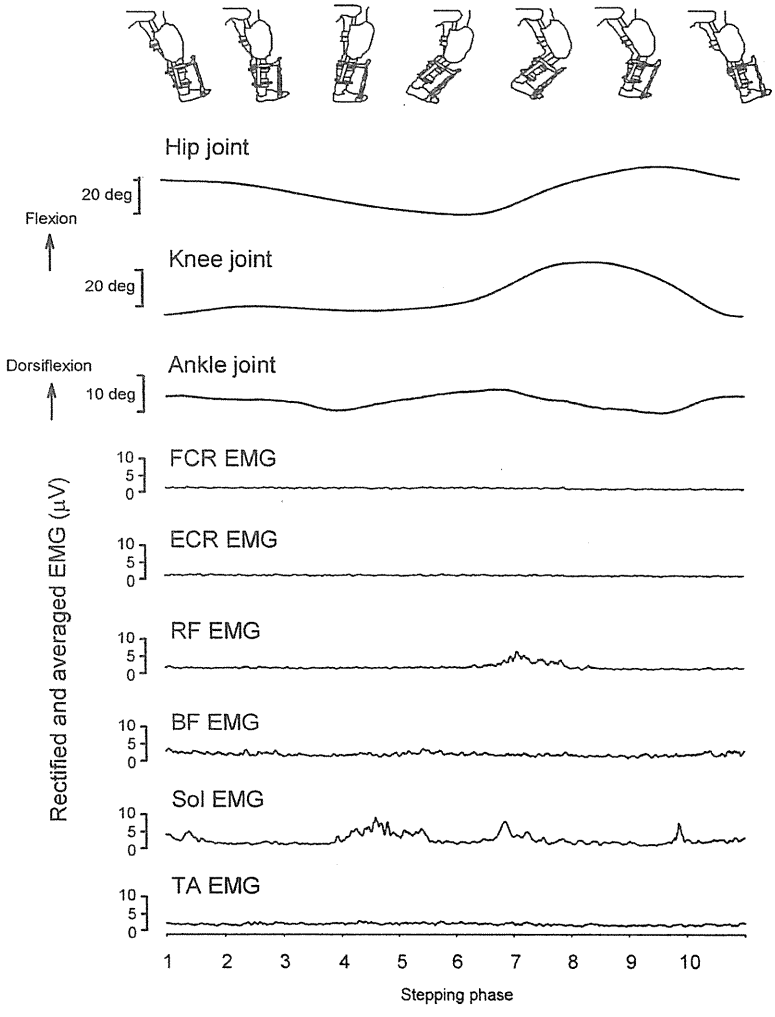

Fig. 1. Typical averaged recordings of joint angle and electromyographic (EMG) activity in the *flexor carpi radialis* (FCR), *extensor carpi radialis* (ECR), *biceps femoris* (BF), *rectus femoris* (RF), *soleus* (Sol), and *tibialis anterior* (TA) muscles obtained from a single subject during driven gait orthosis (DGO) passive stepping. EMG data were full-wave rectified and averaged (12 sweeps). Tracings of the motion of the lower limbare, which were synchronized to the stepping cycle and the joint and EMG data, are shown at the top of the figure.

weight) for a single subject. Because the hip- and knee-joint trajectories were controlled by the robotic-assisted DGO system, joint movements were highly reproducible. Also, the trajectory of the ankle joint was modulated during passive stepping. EMG activities of the FCR, ECR, BF, and TA were quiescent during passive stepping, whereas those of the Sol and RF EMG activities were slightly visible in several stepping phases of this subject.

Figure 2 illustrates the group means of the BG EMG activities obtained from 10 subjects during passive stepping and static conditions. Although the amplitudes of the FCR, ECR, BF, RF, and TA did not change and did not differ significantly across phases and standing conditions [one-way ANOVA: FCR, $F^{(10,90)} = 1.298$, $P > 0.05$; ECR, $F^{(10,90)} = 1.119$, $P > 0.05$; BF, $F^{(10,90)} = 1.179$, $P > 0.05$; RF, $F^{(10,90)} = 0.639$, $P > 0.05$; TA, $F^{(10,90)} = 0.708$, $P > 0.05$], the mean amplitude of the Sol EMG was significantly larger at *phase 5* than during other phases [one-way ANOVA: Sol, $F^{(10,90)} = 3.055$, $P < 0.05$; Bonfferoni post hoc: *phases 2*, *7*, *8*, *9*, and *10*, $P < 0.05$]. However, there was no significant difference between standing and *phase 5* (Bonfferoni post hoc, $P > 0.05$).

Modulation of FCR H-Reflex Amplitude during Passive Stepping

Figure 3 shows representative recordings of the FCR H-reflex during standing and at different phases of passive stepping obtained from a single subject. The amplitude of the FCR H-reflex was suppressed strongly during stepping compared with the standing condition. The suppressive effect on the FCR H-reflex amplitude was seen at all phases of stepping, with little difference based on phase. Figure 4, *A* and *B*, illustrates pooled data for the amplitudes of the FCR H-reflex and M-wave, respectively, obtained from 10 subjects during passive stepping and static standing. Although the amplitudes of the M-wave and BG EMG activities did not differ significantly across phases [compare Fig. 4*B* with Fig. 2*A*; one-way ANOVA: M-wave, $F^{(10,90)} = 0.621$, $P > 0.05$], the mean amplitude of the FCR H-reflex during passive stepping was significantly smaller than those during standing (Fig. 4*A*; Bonferroni test, $P < 0.001$). The one-way RM ANOVA of H-reflex amplitudes revealed a significant main effect for conditions [$F^{(10,90)} = 13.152$, $P < 0.001$]. However, there was no significant difference in H-reflex amplitudes across the stepping phases (Bonferroni test, $P > 0.05$). M_{max} amplitude did not change significantly during the static standing condition and the 10 stepping phases [one-way ANOVA: $F^{(10,90)} = 0.26$, $P > 0.05$].

Figure 5 shows the H-M recruitment curves during standing and at the stance and swing phases of passive stepping obtained from a single subject. It is notable that passive stepping reduced H-reflex amplitudes in the FCR across a wide range of stimulus strengths. Similar results were obtained from eight subjects. Interestingly, the extent of the H-reflex suppression did not depend on the size of the control H-reflex. Figure 6 illustrates the group means of the H-reflex amplitude ($n = 8$) obtained with two different stimulus strengths (i.e., for eliciting the H_{max} amplitude and ~50% of H_{max} during the standing condition). There was a significant suppression of H-reflex amplitude during both the stance and swing phases (Bonferroni test, $P < 0.05$). The two-way RM ANOVA showed a significant main effect and interaction [condition: $F^{(2,14)} = 21.008$, $P < 0.001$; stimulus intensity: $F^{(1,7)} = 31.360$, $P < 0.001$; condition × stimulus intensity: $F^{(2,14)} = 6.718$, $P < 0.01$].

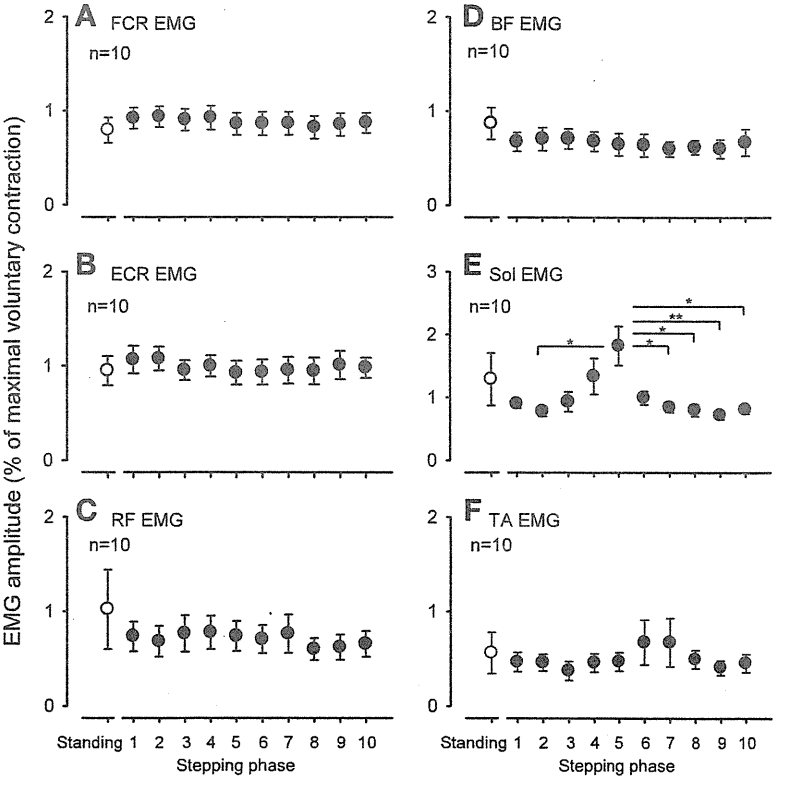

Fig. 2. Grand means (±SEM) of the amplitudes of background EMG activity in the FCR, ECR, BF, RF, Sol, and TA muscles obtained from 10 subjects during standing (open circles) and DGO passive stepping (10 phases; filled circles) conditions (40% unloading of body weight). *$P < 0.05$; **$P < 0.01$.

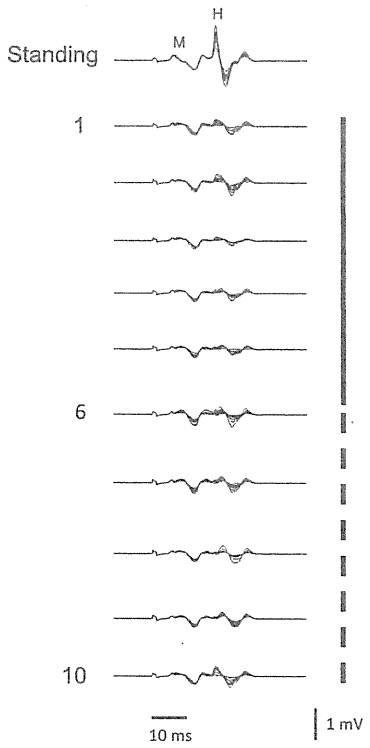

Fig. 3. Typical superimposed recordings (12 sweeps) of FCR Hoffmann (H)-reflex waveforms (H) with a muscle response (M-wave; M) size of ~10% maximal amplitude of the direct motor response (M_{max}) at standing and at 10 phases of DGO passive stepping in 1 subject. Thick, vertical solid and dashed lines indicate stance and swing phases, respectively.

Effect of Load-Related Afferent Feedback on FCR H-Reflex Amplitude during Passive Stepping

We recorded FCR H-reflexes during the stance phase of passive stepping and standing with load (40% unloading of body weight) and with full body-weight support (100% unloading) in 10 subjects. Figure 7, *A–D*, depicts the H-M recruitment curves obtained from a single subject. In both the loaded and unloaded conditions, passive stepping reduced H-reflex amplitudes in the FCR across a wide range of stimulus strengths. Figure 7, *E* and *F*, shows the group means of the amplitudes of H-reflexes during the loaded and unloaded conditions, elicited by two different stimulus strengths—one for eliciting the H_{max} amplitude and the other for ~50% of the H_{max} at control standing. The FCR H-reflex amplitudes at the stance phase, with and without load, were significantly suppressed compared with the respective standing controls (Bonferroni test, $P < 0.05$). The two-way RM ANOVA showed a significant main effect of condition [load: $F^{(1,9)} = 0.095$, $P > 0.05$; condition: $F^{(1,9)} = 31.386$, $P < 0.001$; load × condition: $F^{(1,9)} = 0.717$, $P > 0.05$]; however, there was no significant difference in the reflex amplitudes between the loaded and unloaded conditions.

DISCUSSION

In the present study, we demonstrated that the magnitude of the FCR H-reflex was strongly suppressed during robotic-assisted, passive stepping, compared with that elicited during standing. The suppressive effect on the FCR H-reflex amplitude was seen at all phases of stepping; however, there were no significant phase-dependent differences. Furthermore, the H-reflex amplitudes were suppressed during stepping tasks, both with and without load, with no significant effect of loading itself. These findings suggest that movement-related afferent feedback, rather than load-related afferent feedback, plays a key role in modulating the FCR H-reflex amplitude.

Methodological Considerations

In the current study, the amplitude of the direct M-wave elicited in the FCR was used as an indication of the constancy of the afferent test volley. Similar M-wave amplitudes maintained for all conditions (~10% of maximal M-wave amplitude) are an indication that the activated afferent volley evoked by the various test conditions also remains constant (Fukushima et al. 1982). In fact, there were no significant differences in the M-wave amplitudes among the 10 stepping phases and the standing condition (see Fig. 4*B*).

Although the H-reflex and M-wave amplitudes were normalized to the M_{max} amplitude to mitigate intersubject variability, there is a possibility that the M_{max} amplitude itself differed among step phases (Simonsen and Dyhre-Poulsen 1999) and over the time course of an experiment (Crone et al. 1999). Therefore, the M_{max} in the FCR was recorded at each stepping phase, and predetermined M-wave amplitudes were checked and adjusted carefully with respect to the M_{max} amplitude in each phase. We confirmed that there were no significant differences in the normalized M-wave amplitude during tasks. Thus the suppression of the H-reflex amplitude during passive stepping was not due to changes in the efficacy of the electrical stimulation delivered to the median nerve.

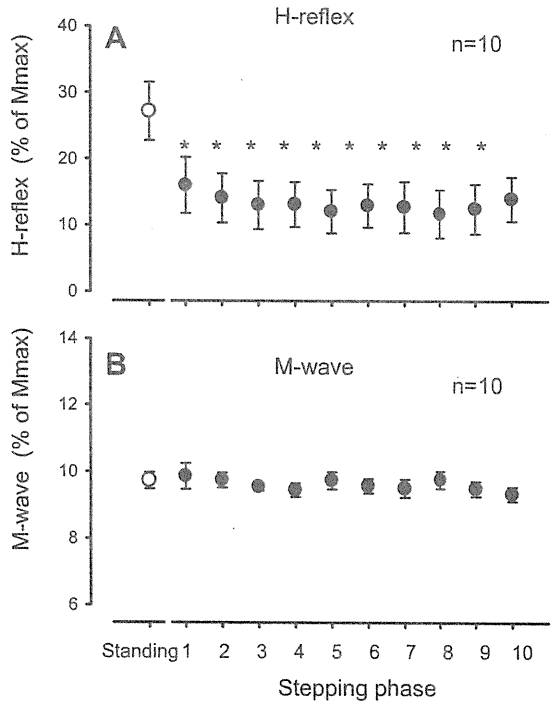

Fig. 4. Grand means (±SEM) of the magnitude of the H-reflex (*A*) and M-wave (*B*) in the FCR muscle obtained from 10 subjects during standing (open circles) and DGO passive stepping (10 phases; filled circles) conditions (40% unloading of body weight). *$P < 0.01$.

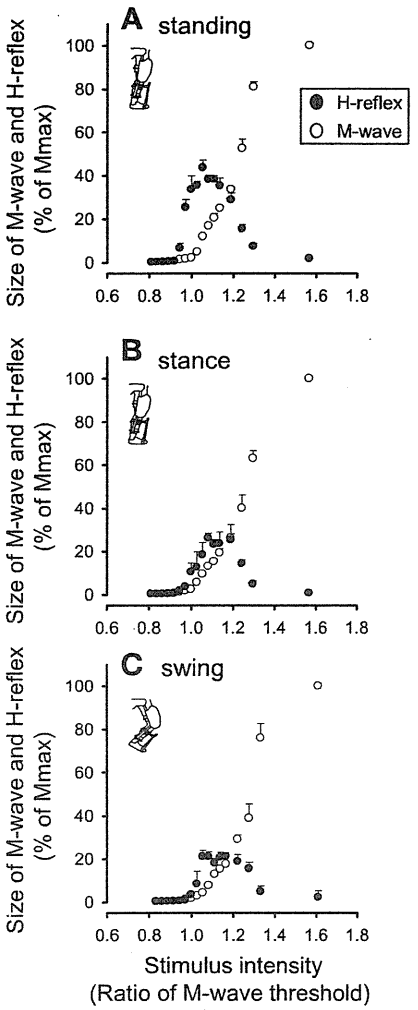

Fig. 5. H-reflex and M-wave (H-M) recruitment curves during standing (*A*) and at the stance (*B*) and swing (*C*) phases of stepping from a single subject. Each plot (H-reflexes, closed circles; M-waves, open circles) shows the mean value (+SD) of 5 responses at each stimulus intensity. Abscissa shows the intensity of the electrical stimulation with respect to the M-wave threshold.

In the present study, intensity of the test electrical stimulation to the median nerve was maintained at ~10% M_{max} in each subject. However, this procedure inevitably required us to use different sizes of test H-reflexes depending on the subject. As it was reported that the degree of the conditioning effect on the H-reflex is proportional to the size of the test H-reflex, it is possible that the responses were affected by the size of the test H-reflex (cf. Crone et al. 1990). However, the H-reflex amplitudes evoked by a wide range of stimulus intensities were suppressed during both the stance and swing phases of passive stepping compared with those during quiet standing (see Fig. 5). Furthermore, when two different stimulus intensities (~50% H_{max} and H_{max} during control standing) to the median nerve were investigated, there was a significant suppression of H-reflex amplitudes at both the stance and swing phases of passive stepping for both stimulus intensities (see Fig. 6). Thus it is likely that the extent of amplitude suppression did not depend on the size of the test H-reflex (cf. Crone et al. 1990).

Reciprocal inhibitory effects arising from the forearm extensor muscles may possibly also affect the amplitude of the FCR H-reflex (Day et al. 1984). However, the amplitude of the ECR EMG activity was kept to a minimum (see Fig. 2*B*), and there were no significant differences across conditions during our DGO stepping and static standing. Thus suppression of the FCR H-reflex during passive stepping cannot be ascribed to a change in antagonist muscle activity.

Possible Sources of the FCR H-Reflex Suppression during Passive Stepping

Our finding that passive stepping suppressed the magnitude of the forearm H-reflex is well in line with previous reports (Frigon et al. 2004; Loadman and Zehr 2007; Zehr et al. 2007) of conditioning by remote rhythmic movement. However, one possible discrepancy between our study and previous ones is the possible substantial contribution of the voluntary drive to maintain rhythmic leg movements. Although subjects were instructed to relax and allow the DGO to drive lower-limb movements, complete passive stepping was difficult to achieve. In fact, slight Sol EMG activities [~1–2% of maximal voluntary contraction (MVC)] in the late stance phase were found and were significantly larger than those during other phases (see Figs. 1 and 2). These small Sol EMG activities during loaded stepping were also observed in our recent studies (Kamibayashi et al. 2009, 2010), even though the subjects were asked to relax. In addition, the ankle joint was held by foot lifters (spring-assisted elastic straps) to prevent foot drop and thereby restricting the trajectory of the ankle joint. Under this situation, an increase in EMG activity in the Sol at *phase 5* might be a stretch-induced muscle activity, signifying that they are involuntary in nature. During normal walking, generally, it has been demonstrated that the peak EMG value of the Sol muscle was above 80% of MVC (Arsenault et al. 1986; Nishijima et al. 2010). In our situation, leg EMG activities (~0.5–2% of MVC) during DGO stepping were extremely low compared with during normal walking. Also, reciprocal EMG activity in TA was barely discernible (see Figs. 1 and 2). Therefore, it may be that the contribution of descending commands to suppression of the FCR H-reflex during DGO-driven stepping was extremely small compared with during normal

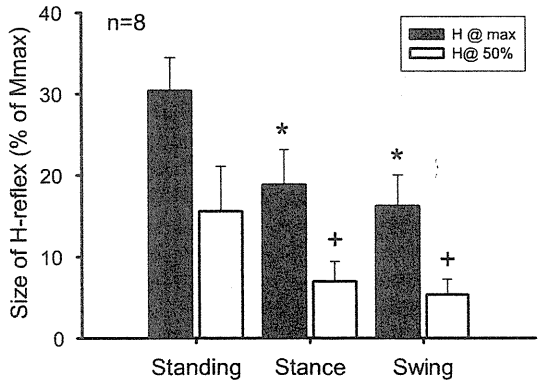

Fig. 6. Group means of the H-reflex amplitudes during standing and the stance and swing phases of passive stepping. Two different intensities of electrical stimulation were used—the intensity that elicited the maximal H-reflex (H_{max}) amplitude (black bars) and that elicited an amplitude of ~50% of H_{max} (gray bars) during standing. *, +$P < 0.05$, significantly different from the respective control (standing) values.

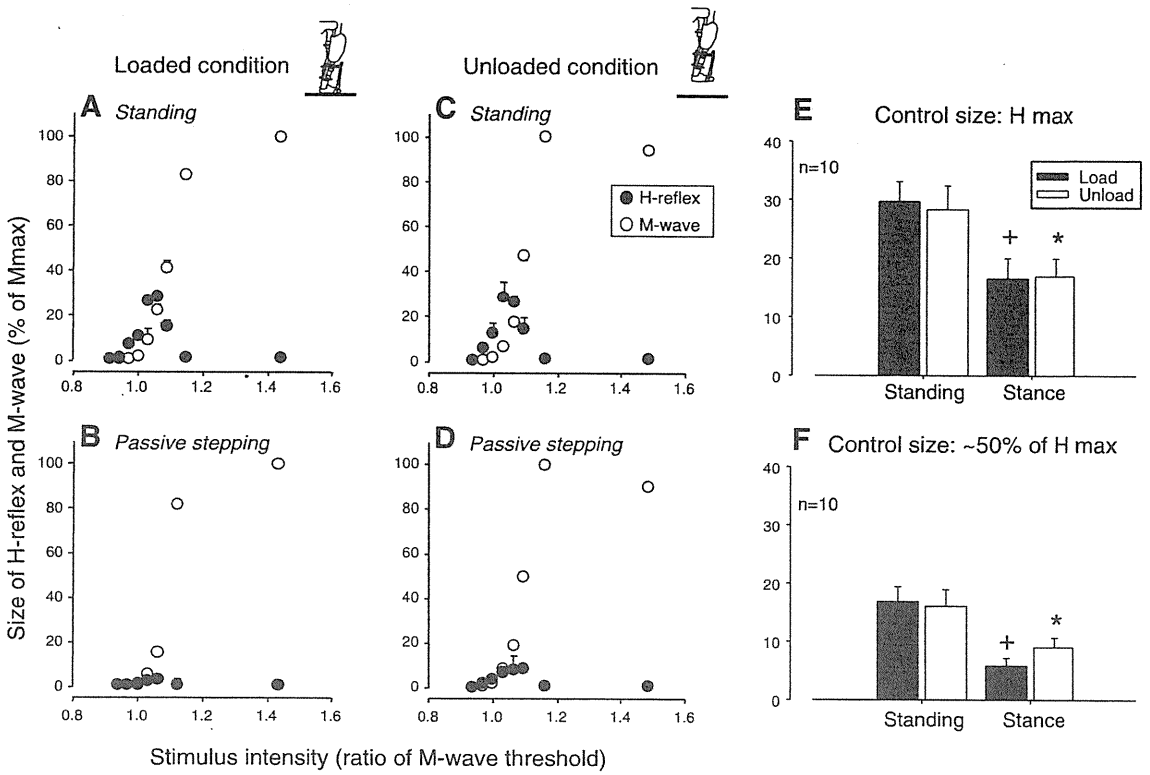

Fig. 7. Effect of loading on the FCR H-reflexes during standing and DGO passive stepping in 10 subjects. H-M recruitment curves at standing (*A* and *C*) and passive stepping (*B* and *D*), with load (40% unloading of body weight; *A* and *B*) and without load (100% unloading; *C* and *D*) obtained from a single subject. *E* and *F*: group means of H-reflex amplitudes with (black bars) and without (gray bars) load. Two different stimulus strengths were used to elicit the H_{max} amplitude (*E*) and ~50% of H_{max} (*F*) while standing. *, $+P < 0.05$, significantly different from values during the respective standing conditions.

walking. Furthermore, even while performing isolated knee or hip passive movements of the ipsilateral leg with the same DGO system, the magnitude of the FCR H-reflex did not show any suppression compared with during quiet standing (T. Nakajima and T. Kitamura, unpublished observations). Delwaide and Toulouse (1981) previously demonstrated that stretch reflex amplitudes in the leg muscle were not suppressed by passive, discrete wrist movement in the remote muscle. Taking all of these observations into consideration, we favor the explanation that stepping-related afferents arising from combined joint movements in both legs play a key role in generating suppression of the FCR H-reflex amplitudes during our DGO stepping.

We further investigated the effect of load-related afferent feedback on the FCR H-reflex amplitude during the stance phase of passive stepping and standing. During locomotion, inputs from load-related receptors are important for the neural control of locomotion (Dietz et al. 2002; Duysens et al. 2000; Pearson and Collins 1993; Shoji et al. 2005; Stephens and Yang 1999; Van de Crommert et al. 1998). The potential mechanoreceptors include those in muscles, skin, and joints from both legs (Duysens et al. 2000). In fact, we have observed strong facilitation of the cutaneous reflex in the TA muscle during the late-stance to early-swing phase of passive loaded stepping but not during passive unloaded stepping (Nakajima et al. 2008). More recently, we investigated the effect of body load on the amplitude of the H-reflex in the Sol muscle using the same DGO system (Kamibayashi et al. 2010) and found that the Sol H-reflex was equally suppressed by passive stepping, both with and without body loading. This was also true in the current study for the suppression of the FCR H-reflex during passive stepping (see Fig. 6). In addition, load-related afferent feedback during rhythmic arm movement was shown to have no influence on Sol H-reflex suppression in the stationary leg (S. R. Hundza, G. C. de Ruiter, and E. P. Zehr, unpublished observations).

Based on these findings, it is unlikely that load-related afferent feedback contributed to the suppression of FCR H-reflex amplitude during passive stepping in our experimental situations [e.g., our population of subjects and number of subjects (n = 10)].

Lack of Phasic Reflex Modulation in the FCR during Passive Stepping

We found that movement-related afferent feedback from both legs does not produce a phase-dependent modulation of the FCR H-reflex (see Figs. 3 and 4). Indeed, the specific source of the modulation is not certain, although these findings may indicate that the phasic afferent inputs arising from passive leg movements are conveyed to the ascending, long propriospinal neurons responsible for the inhibition of the monosynaptic reflex arc in the other segments of the spinal cord (Alstermark et al. 1987; Cheng et al. 1998; Dietz 2002; Frigon et al. 2004; Loadman and Zehr 2007; Misiaszek et al. 1998; Zehr and Duysens 2004). More recently, de Ruiter et al. (2010) reported that suppression of the Sol H-reflex amplitude

was dependent on the phase of movement during active arm cycling. Probably descending commands accompanying active arm cycling generate phasic modulation of the H-reflex during remote rhythmic movement. Based on these and our findings, it is likely that afferent information for stepping plays an important role in generating tonic suppression of the H-reflex amplitude in remote muscles (Cheng et al. 1998; Misiaszek et al. 1998; Sasada et al. 2010). These features of the general suppression of forelimb reflex excitability during passive leg stepping can be explained by the afferent-induced presynaptic inhibition on the Ia terminals of the FCR H-reflex circuitry during locomotor activity (Cheng et al. 1998; Frigon et al. 2004; Misiaszek et al. 1998; Sasada et al. 2010; Zehr and Duysens 2004). This discussion is based on indirect evidence in humans (Frigon et al. 2004; Zehr et al. 2007), and further study is needed to determine the possible contribution of presynaptic inhibition on suppression of the H-reflex pathway during passive movement of the remote limb. In addition, further investigation is needed to elucidate the functional implication of walking-related afferent signals on remote H-reflex suppression during walking.

It has been suggested that it is possible to regain locomotor abilities after spinal cord injury with intense stepping training on a treadmill (Dietz et al. 2002; Van de Crommert et al. 1998). As a translational implication for rehabilitation, our findings suggest that there may be a potential therapeutic use for passive stepping in the management of spasticity in remote muscles after spinal cord injury and stroke (cf. Hundza et al. 2009; Zehr and Duysens 2004; Zehr et al. 2009). In fact, a relationship has been seen between spasticity and hyperexcitable reflexes (e.g., H-reflexes; Levin and Hui-Chan 1993); however, specific studies designed to test this hypothesis are needed.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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2011年／第48回 日本リハビリテーション医学会 学術集会／千葉

《会長講演》

物性・構造の“Manufacturing”
—人体の組織改変を人為的に起こす—*

第48回日本リハビリテーション医学会学術集会 会長　赤居　正美
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はじめに

第48回日本リハビリテーション医学会学術集会開催に当たり，会長講演としてこれまでの研究内容を話す機会が与えられたので，ここに紹介させていただきたい．

私は卒業後，整形外科医として卒後研修を開始し，途中からリハビリテーション（以下，リハ）科医に移るという経歴をたどったが，基本的には運動器疾患を扱ってきた．

骨折治癒・組織修復促進の試み
—機械系としての骨・靱帯などの物性—

研究面では，整形外科ということもあり，hardwareとしての骨や靱帯の物性を扱うことが多かった．そこで骨折の癒合や靱帯損傷の治癒促進に関心を持ち，力学刺激や電磁場といった各種の物理刺激による組織改変をテーマに選ぶこととなった．細胞の様々な機能発現には，メカニカルストレスに代表される周囲からの物理的刺激が重要な役割を果たしているというのが前提であった．考えた作業仮説としては，①適切な刺激が加わり続けることが代謝維持に不可欠とすれば，②外部から運動系への働きかけを用いることにより，③固定・安静による運動器官の廃用性変化の軽減・予防を目指すことができるのでは？ ④さらには機能向上につなげることも可能なのでは？ といった流れを想定した．

創外固定による脚延長やtissue expansionなどのより直接的，侵襲的な手法も当時，発展しつつあったが，私の関心はもっぱら細胞組織での「刺激信号制御」を介しての間接的な方向であった．当時，骨の圧電現象や骨細管表面における流動電位などの知見もあり，動物実験を中心に電気刺激を介入手段として組織修復の促進を調べた．

外から電磁場を加えると，生体組織内では超低周波の電場が形成され，荷電粒子（イオン）の移動つまり電流を生じる．従来の報告では，周波数は概ね300 Hz以下，電場強度としては生体レベルで0.1～10 V/m，細胞レベルではより微弱な10^{-6} V/mに至る数字が挙げられる（図1）．低周波領域での細胞膜の絶縁性は極めて高いので，外部刺激に由来する界面電位の変化はそのままでは細胞内には影響しないと考えられる．イオンチャネルやレセプターなどの膜の特定部位で何らかの透過性変化をもたらし，スイッチ機構を変えるらしい．細胞表面の局所環境の変化は，細胞膜を介して細胞内の情報伝達機構と結び付き，外因性の

* 本稿は第48回日本リハビリテーション医学会学術集会会長講演をまとめたものである．（2011年11月2日（木），幕張メッセにて）

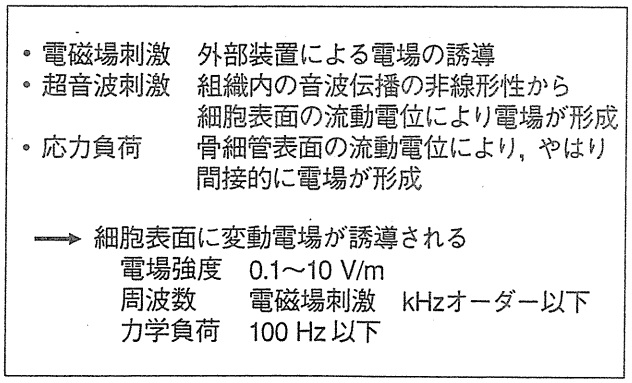

図1　Pillaによる物理刺激統一機序の提案

刺激下に，転写・翻訳レベルでの亢進，DNA・蛋白合成の増加といった核内の遺伝子発現に至る．その具体的機序は未だ不明であるものの，細胞膜の電気的特性とイオンなどの荷電粒子との関連で，超音波治療などの効果も包含した物性物理学の法則に基づく理論モデルも提案されている[1]．電気刺激，超音波，低出力レーザの臨床応用に関するメタアナリシスの報告もある[2~4]．

脊髄損傷の不全麻痺改善の試み
—制御系としての神経回路・システムの機能—

その後，関心は骨・関節や靱帯といった機械系から，softwareとしての神経制御系，システムとしての神経系回路の改変，言い換えれば可塑性に移っていった．中枢神経系の可塑性と言えばまず脳が対象になるのであろうが，四肢を対象にあれこれ実験をしていたせいか，同じ中枢神経系でも脊髄を対象とすることになった．多くの脊髄損傷患者と接する機会があったためでもあろう．そうするうちに再生医学，脳科学など関連する医学領域での発展は目覚ましく，中枢神経系での可塑性に注目し，リハ訓練と結びつくことで新たな可能性を示すようになった．細胞レベルの修復が機能改善につながるためには，その後の神経回路の再構築が不可欠である．反復訓練による運動学習やリハ訓練が神経回路の再構築，すなわち“可塑性”，“再学習”を促すことが判ってきたのであった[5]．

不全脊髄損傷に対する歩行訓練において，ヒトの歩行動作における脊髄内の歩行中枢（central pattern generator：CPG）の存在が前提となっている[6]．幸いにして本邦第一例としてLokomatという訓練装置を導入できた．こうした体重免荷式歩行訓練装置はCPGを賦活化する手法として考えられている．しかしながら，現在行われている体重免荷式歩行訓練には，①訓練方法（Lokomatの使用方法も含め）にばらつきがある，②CPGを賦活化するというコンセプトはあるものの，それ以上のメカニズムが明らかでない，③受傷後1年以内の訓練効果は自然回復の影響があり，他の訓練効果と識別しにくい，④受傷後1年以降だと訓練効果が出にくい，などの課題がある[7~9]．そこで，体重免荷式歩行訓練のメカニズムを明らかにするために

・受傷後1年以上経過した症例を対象とする．
・CPG賦活化の方法を検討する．
・訓練前後で得られる歩行の変化を詳細に解析する．

との手法で研究を進めている．

健常者，小児，対麻痺患者での知見から，荷重や股関節周囲からの求心性入力が歩行中の下肢筋活動パターンに必須とされており，伸筋からの固有受容器入力と足底からの荷重情報としての力学受容器入力がそれらを担っているのであろう．荷重レセプターからの信号は多シナプス脊髄反射路へ統合され，床面の状態にプログラムされた歩行パターンを適合させる．しかし皮質脊髄路における上位との結合性の強弱，中枢における随意努力の有無といった制御的な要素も関連するらしい（図2）．なかでも中枢からの下降指令における「集中」の存在はそれまでの訓練プロトコルの変換を迫るものであった．我々はCPGを賦活するのに留まらず，皮質脊髄路全体の促通を図っているようである．

部分免荷式歩行訓練が不全脊髄損傷患者の歩行機能に及ぼす作用メカニズムを解明することで，その適応が明確になり，また訓練技術の向上につながると期待できよう．