Reflex modulation during rhythmic limb movements in humans

Tomoyoshi Komiyama1,2* and Tsuyoshi Nakajima3

1 Department of Health and Sports Sciences, Faculty of Education, Chiba University, Chiba 263-8522, Japan
2 Division of Health and Sport Education, The United Graduate School of Education, Tokyo Gakugei University, Tokyo 184-8501, Japan
3 Department of Integrative Physiology, Kyorin University, School of Medicine, Tokyo 181-8611, Japan

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Abstract
For many locomotor behaviors, such as walking or running, we count on subliminal somatosensory information to smoothly maintain on-going movement and avoid falling down when disturbances are presented to the stability of the body. Reflex responses induced by disturbances to stability play important roles in generating quick corrective responses. Reflex outputs to the arm and leg muscles generated by muscle and cutaneous afferents during locomotor movement show quite different features compared to those generated by simple voluntary contraction during sitting or standing, irrespective of the similar background activity of motoneurons. In particular, the excitability of cutaneous reflex pathways elicited by the electrical stimulation of low threshold mechanoreceptors on the skin is strongly modulated in a phase-, nerve-, task-dependent manner during locomotor movement. The pattern generating system in the spinal cord, which has been studied intensively in quadrupedal animals, may be responsible for both generating locomotor movement and reflex modulation even in humans. However, due to methodological difficulties, the accumulated evidence derived from human experiments is indirect. In this review, we will outline these unique features of the cutaneous reflexes during locomotor and rhythmic movements in humans.

Keywords: reflex modulation, rhythmic limb movements, central pattern generator, walking, cycling, cutaneous reflexes

Introduction
Around a century ago, original physiological evidence indicating the possible contribution of neural connections subserving intralimb and interlimb reflexes to locomotion was provided by Sir Charles Sherrington with decelerated cats1,2). Later, it was shown in cats that stimulation of the cutaneous nerve produces general flexor excitation with the exception of muscles directly beneath the stimulated region of the skin. This reflex pattern was named “local sign”3), and produces withdrawal responses to direct the limb away from noxious cutaneous stimuli4). Noxious reflexes are therefore thought to be indicative of a modular organization of the spinal cord to produce a seminal functional outcome during locomotion in response to noxious sensation5).

Different from the noxious reflexes, cutaneous afferents arising from low threshold mechanoreceptors existing under the skin surface can give rise to widespread and segmental excitatory and suppressive reflex effects in various motoneuron pools (cutaneous reflexes for review, see6-8)). To date, the cutaneous reflexes in human hand muscles have been demonstrated to be modulated in a task-, age- and pathological-dependent manner9-13). Interestingly, the functionally relevant reflexes occur during human walking14,15). In this review, we will discuss the nature and functional significance of the intralimb and interlimb cutaneous reflexes during locomotor movements in humans. In addition, modulation of monosynaptic spinal reflex (Hoffmann (H-) reflex) during rhythmic movement will also be discussed as necessary.

Methodological considerations
1. Neurophysiological bases of reflex responses arising from cutaneous afferents
Cutaneous reflexes in first dorsal interosseous (FDI) are triphasic, consisting of an initial short latency excitation (E1), followed by inhibition (I1), then followed by a prominent long latency excitation (E2). An electrophysiological estimation of the central delay and the ascending and descending conduction time of E1 and E2 suggests that they are mediated by distinct reflex pathways11,12). In particular, E2 is absent in patients with damage to the motor cortex, but E1 remains in these subjects. In addition, E2 is reduced in amplitude and often delayed in patients
with motoneuron disease causing damage to the corticospinal tract. From these observations, it was concluded that E1 has a spinal pathway; and E2 is of supraspinal origin requiring transmission of afferent impulses through the dorsal columns, a relay in the sensorimotor cortex, and descending transmission to the lower motoneuron pool by way of the corticospinal tract. To date, cutaneous and descending transmission to the lower motoneuron requires transmission of afferent impulses through that E1 has a spinal pathway; and E2 is of supraspinal circuitry.

Cutaneous reflexes can be elicited in leg (hindlimb in quadrupeds) muscles as well. Contact between the dorsum of the hindlimb paw and an obstacle during the swing phase of locomotion in the cat evokes coordinated ankle flexion and knee extension in an attempt to avoid tripping. These reflex patterns have been termed “stumbling corrective reaction”. Also, coordinated muscle activation in intra- and intersegments following stimulation of the skin during on-going locomotor activities was shown in cats. Similar reflex patterns are observed in forearm, upper arm and leg muscles following the stimulation of cutaneous nerves in humans. Short latency excitatory responses are usually very small and sometimes indiscernible in sitting or quiet standing postures. However, short latency excitatory responses are facilitated when subjects stand on an unstable surface, suggesting that the short latency component of the cutaneous reflex in leg muscles is strongly modulated in a context-dependent manner. It is worthy to note that the cutaneous reflexes at a given latency can be reversed from excitatory to inhibitory depending on phase or task.

Reflex reversal is thought to be an outcome of parallel inputs to motoneurons from distinct excitatory and inhibitory interneurons, which receive excitatory inputs from both descending and ascending systems. In addition, these discrete reflex pathways would be differentially regulated depending on a given task. To date, there is no tangible evidence showing that the short latency cutaneous reflexes in leg muscles are mediated solely by spinal circuitry.

Recent advances in the study of interlimb reflexes in humans have provided ample evidence suggesting that cutaneous reflexes are crucial for generating rapid compensatory movements in remote limbs in response to a sudden disturbance of limb movement during various locomotor activities. Intralimb cutaneous reflexes have been demonstrated to possess task dependency (phasic locomotor vs. tonic maintained activity), intensity dependency (noxious vs. non-noxious stimulation), load dependency, phase dependency (swing vs. stance), and laterality dependency (ipsilateral vs. contralateral effects). The amplitude of cutaneous reflexes in both arm and leg muscles strongly depends on the location of the skin in which the stimulation was delivered (location specificity). These previous studies indicate that cutaneous reflexes are of functional importance for a variety of rhythmic movements for on-going activity in response to tactile sensation. In addition, distinct reflex patterns during stationary contraction and locomotor activity strongly suggest an involvement of pattern generating systems in limb muscles, as has been observed in quadrupedal animals.

2. Pattern generating system

Locomotor activities such as walking, running and swimming involve distinct rhythmic patterns of arm and leg motions. In a considerable number of invertebrate and vertebrate preparations, neuronal activity related to central pattern generating (CPG) circuits in the spinal cord for rhythmic locomotor movement has been identified. Brown first demonstrated a neural system in the lumbar spinal cord that generated oscillation of alternative flexor and extensor activity. The neural center, termed “half-center”, is thought to be a key system for CPG, which produces the basic locomotor rhythm. CPG produces alternative flexor and extensor activity without input from descending motor and ascending sensory inputs because locomotor rhythm can be generated in deafferented and spinalized (fictive locomotion) preparations. Therefore, the term CPG should be used only to refer to spinal circuits capable of generating an organized bilateral rhythmic pattern in the absence of descending and sensory inputs. Indeed, in acutely spinalized and paralyzed cats, a well-organized rhythmic output can be recorded directly from flexor or extensor nerves with pharmacological stimulation (L-DOPA) in the complete absence of overt movement. As shown in Fig. 1, a given level of the spinal cord involves some key features of locomotor control, consisting of CPG, several descending pathways such as corticospinal and reticulospinal tracts, neurochemically defined pathways that release neuromodulators such as norepinephrine (NE) or serotonin (5-HT), and afferents from peripheral sensory receptors.

Contusion and pharmacological preparations were used to determine the seminal localization of rhythogenesis in the spinal cord. Although rhythmicogenetic properties within the lumbosacral spinal cord are distributed over several segments, the L3-L4 segments in cats and L1-L2 segments in rodents are critical for rhythm generation. Inactivating or damaging these segments will generally abolish or severely impair locomotion. In contrast to the lumbar enlargement, Ballion et al. found a caudo-rostral gradient for rhythogenesis in the cervical enlargement of isolated neonatal rat spinal cord. Juvin et al. suggested that while C5 through C8 are rhythemogenic, they can be driven by the lumbar pattern generating circuitry in a longitudinally intact preparation. A number of authors have proposed that long propriospinal axons are likely candidates for the functional coupling of the cervical and lumbar CPG networks and the mediation of interlimb coordination.

Electrically stimulating the pyramidal tract during fictive locomotion in the adult cat can reset the hindlimb
rhythm, indicating that the corticospinal tract has direct access to the rhythm-generating circuitry. In addition, group I ankle extensor afferents from the foot appear to have direct access to the rhythm-generating circuitry of the spinal locomotor CPG, which was inferred by their ability to reset or entrain the fictive locomotor rhythm in adult cats. Cutaneous inputs from the plantar surface of the paw can also reinforce extensor activity in decerebrate cats walking on a treadmill or during fictive locomotion. The results of these studies indicate that CPG receives various inputs from the descending and ascending system and can be modulated in concert with the locomotor environment or task requirements.

CPG not only acts as a generator of basic locomotor rhythm, it also plays a crucial role in regulating the gain of reflex pathways, which gives rise to quick corrective behaviors in response to somatosensory inputs. The higher motor center likely sends driving commands to CPG; and, then, the gain of many reflex pathways is regulated by CPG to cope with the various modes of disturbances through the somatosensory system.

3. Common core system generating rhythmic movement and modulator for reflex pathways

Human subjects can perform a wide range of rhythmic arm and leg movements easily, which is beneficial in adapting to different physical or environmental constraints during locomotion. For a basic stratagem to persist locomotion in different environments, the brain must select an optimal movement pattern and trigger descending commands that converge to subcortical regions such as the cerebellum, basal ganglia and brain stem to shape the required motor program. Of these, the meencephalic locomotor region (MLR) in the midbrain plays a crucial role in generating basic oscillatory signals for rhythmic limb movements. Signals from the MLR are known to drive the CPG in the spinal cord. In addition, group I ankle extensor afferents from the foot appear to have direct access to the rhythm-generating circuitry of the spinal locomotor CPG, which was inferred by their ability to reset or entrain the fictive locomotor rhythm in adult cats. Cutaneous inputs from the plantar surface of the paw can also reinforce extensor activity in decerebrate cats walking on a treadmill or during fictive locomotion. The results of these studies indicate that CPG receives various inputs from the descending and ascending system and can be modulated in concert with the locomotor environment or task requirements.

Fig. 1 General framework of locomotor control as described by Rossignol and Frigon. F and E, flexor and extensor motoneurons; DLF, dorsolateral funiculus; VLF, ventrolateral funiculus; NE, noradrenaline; 5-HT, serotonin; GLU, glutamate; Ach, acetylcholine; DC, dorsal columns; DRG, dorsal root ganglion. For detailed explanations, see Rossignol and Frigon.
investigate the role of CPG as a modulator of somatosensory reflexes depending on the objective of the research. If possible, changes in load using counter weights, water immersion, and changes in axial resistance load can be used to investigate the nature of the CPG system in humans\(^{67,69,63}\).

4. Differential regulation of the excitability of the motoneuron pool and reflex pathways during static muscle contraction and rhythmic movements

During stationary contraction, the excitability of spinal reflexes are automatically tuned in accordance with the level of motoneuronal excitability\(^{64}\). However, during rhythmic movements, the gain of monosynaptic spinal reflexes is differentially regulated from the excitability of the motoneuron pool for the homonymous muscle. Brooke et al. conducted extensive research examining the regulation of reflex pathways during passive cycling or stepping in humans. They showed that passive movement of the leg in a pedaling motion leads to a profound inhibition of the reflex in the moving leg and the contralateral leg at rest\(^{65-67}\). They also showed that the magnitude of H-reflex inhibition was dependent on the phase position and the estimated rate of stretch of the extensors of the knee and hip. They showed that an increasing speed of passive rotation increased the inhibition at all positions, but was most pronounced near the fullest flexion of hip and knee. Pedaling-like passive movement of merely the hip or knee joint also results in substantial inhibition of the reflex\(^{61,65}\). The results of these studies suggest that activation of somatosensory afferents, likely from muscle mechanoreceptors excited by the movement, leads to the inhibition of reflex transmission, which appears to be irrelevant of the excitability of the motoneuron pool. Thus, afferent inflow from muscle spindles to the motoneuron is confined by premotoneuronal mechanisms, most probably by presynaptic inhibition driven by the CPG system during leg pedaling tasks.

In leg muscles, cutaneous reflexes following sural nerve stimulation are strongly modulated in a phase-dependent manner depending on the biomechanical function of the limb muscles during cycling\(^{69}\). Also, modulation of the H-reflex and cutaneous reflexes evoked in forearm muscles are dependent on the movement phase during rhythmic arm movement\(^{29,30}\). Furthermore, although the size of the reflexes is proportional to the background EMG in a stationary condition, the relationship becomes ambiguous during cycling\(^{21,30,69}\). One of the underlying mechanisms for these reflex modulations may be regulation at the premotoneuronal level. Frigon et al.\(^{70}\) demonstrated that sural nerve stimulation facilitated H-reflexes in the soleus (Sol) at shoulder extension, but not at shoulder flexion during static and arm cycling, and that common peroneal nerve (CP) stimulation significantly reduced Sol H-reflex amplitude during static and cycling tasks (see Fig. 3). Reflexes in the soleus when sural and CP nerve stimulation were delivered alone, did not differ between cycling and static trials. Thus, it is likely that the task-dependent changes in H-reflex amplitude are irrelevant to motoneuron excitability. Therefore, the modulation occurred at a pre-motoneuronal level, probably by presynaptic inhibition of the Ia afferent volley. It may be that neural networks coupling the cervical and lumbosacral spinal cord in humans are active during rhythmic arm movement, and activation of these networks may assist in reflex linkages between the arms and legs during locomotor tasks. These results suggest a contribution of the pattern generating system in the spinal cord to the regulation of locomotor activity not only in the legs, but also in the arms. Taking together, rhythmic arm and/or leg cycling can be used as a tool for investigating the function of CPG in humans.

**Reflex modulations of cutaneous reflexes in arm muscles during rhythmic movements**

In humans, the evolution of an upright stance and bipedal gait has allowed for a great deal of flexibility in how the arms interact with each other and how combined arm and hand action can manipulate objects. At the same time, cortical control of arm muscles has been largely consolidated in the process of evolution with strengthening the monosynaptic connections between pyramidal tract cells and both motoneurons and propriospinal neurons located at C3-C5 segments\(^{71}\). Also, the reflex system is differentially organized between arm and leg to adapt to different environmental and biomechanical requirements. In particular, CPG regulation of the reflex system for arm and leg may be differentially organized because of their functional differences in manipulation and locomotion\(^{72}\). However, evidence suggests that there are some similarities and dissimilarities of reflex control between the arms and legs during cyclic movement.

![Fig. 2 Schematic conceptual overview of the regulation of rhythmic human movement provided by Zehr et al.\(^{62,77}\)](image)
1. Reflex modulations during arm cycling

The CPG system in humans may contribute as much to the control of rhythmic arm movement during locomotor movement as it does to cyclic leg movement. The rhythmic arm swing during human locomotion has been suggested to be a functional outcome resulting from muscle activation, and not a passive pendular movement due to mechanical interaction with leg and trunk motion73-75. Recent locomotor research in humans suggests that CPG plays an important role in generating muscle activation and in reflex regulation of arm movements, and may share common features with those in quadrupedal animals6,8,76-78).

It has been documented that, during rhythmic arm movement, the cutaneous reflex amplitude follows stimulation of the superficial radial nerve co-varied with background EMG (background-dependent modulation)79). This is in contrast to the pattern seen in the leg muscles in which there is often a dissociation between reflex amplitude and EMG level14,80). Later, however, a significant background dependency could not be demonstrated30,81,82). In some arm muscles, the position of the limb during arm cycling influenced the size of the cutaneous reflex responses in a manner that was independent of the background EMG activity. The middle latency cutaneous reflexes were facilitatory during static contraction, but attenuated dramatically. In addition, cutaneous stimulation resulted in an excitatory response at some points in the arm cycle, but inhibition at other points of the cycle (reflex reversals)30). Reflex reversals also occurred in some

Fig. 3 Modulation of H-reflex in the soleus during arm cycling, and effects of somatosensory conditioning stimulation. Conditioning stimulation to the common peroneal nerve (CP) and sural nerve stimulation suppresses and facilitates the H-reflex amplitude during arm cycling. For detail, see Frigon et al.70).
muscles between static contractions and rhythmic movements. Reflex pathways mediating the cutaneous reflex may receive parallel excitatory and suppressive inputs, and are under the control of descending and ascending systems in addition to the CPG system (see Fig. 1 and 2). Thus, the reflex outputs are flexibly modulated in a phase-dependent, posture-dependent, nerve-specific, task-dependent and context-dependent manners. It is important to consider these factors when interpreting the functional significance of cutaneous reflexes during the variety of rhythmic arm movements.

2. Left-right coupling of arms during rhythmic movement

Muscle activity on the left and right side of the body is precisely coordinated during locomotion to secure alternation of corresponding muscles on either side of the body as seen during walking. The neuronal circuits responsible for left-right coordination are commissural interneurons, whose axons cross the midline via the ventral commissure and which have been studied extensively in the rodent and cat spinal cord. A dual intrasegmental commissural interneuron (sCIN) system was demonstrated that inhibits segmental motor neurons via polysynaptic inhibition. Polysynaptic inhibition is mediated by glutamatergic sCINs and local ipsilaterally-projecting inhibitory interneurons, including Renshaw cells and Ia inhibitory interneurons; and monosynaptic inhibition is mediated via glycinergic/GABAergic sCINs. In addition to the inhibitory pathways, glutamatergic sCINs can excite motor neurons directly. In humans, the nature of coupling between CPGs for the left and right arms is of significant interest as a basis for comparison of the mechanisms of neural control between arm and leg movements. It was reported that H-reflexes are not depressed in a stationary arm when the contralateral arm is moved in a cyclical manner, which clearly differed from the regular depression of cutaneous reflexes in leg muscles after stimulation of cutaneous nerves in the foot during forward and backward walking, which appears to be further evidence for CPG activity contributing to neural activation and reflex modulation during rhythmic arm movement. Thus, control mechanisms underly the modulation of cutaneous reflex amplitude in arm muscles during rhythmic arm movement are thought to be similar to those reflex modulations in the leg. These findings suggest that cutaneous reflexes are under similar control of CPG in the upper and lower limbs, which implicates similar motor control mechanisms under the variety of locomotor constraints.

Modulation of cutaneous reflexes in leg muscles during walking and cycling

Cutaneous reflexes, particularly those arising from stimulation of the sural nerve (innervating the lateral border of the foot), the tibial nerve (innervating the ventral foot surface) and superficial peroneal nerve (innervating the dorsal surface of the foot), have been studied extensively in humans and have shown phase- and task-dependent modulation of cutaneous reflexes occurring at restricted latencies. Initially, the extent of modulation of the

3. Similarity of modulation of cutaneous reflexes in arm and leg muscles during arm cycling

Once the arm begins rhythmic cyclical movement, the amplitude of cutaneous reflexes recorded from muscles in the moving arm is strongly modulated in a phase- and task-dependent manner. In addition, amplitudes of both early and middle latency cutaneous reflexes are modulated similarly, irrespective of arm cycling direction (forward or backward cycling). That is, at similar phases in the movement cycle, responses of corresponding sign and amplitude were observed regardless of movement direction. In general, these findings are parallel to observations in leg muscles after stimulation of cutaneous nerves in the foot during forward and backward walking, which appears to be further evidence for CPG activity contributing to neural activation and reflex modulation during rhythmic arm movement. Thus, control mechanisms underlying the modulation of cutaneous reflex amplitude in arm muscles during rhythmic arm movement are thought to be similar to those reflex modulations in the leg. These findings suggest that cutaneous reflexes are under similar control of CPG in the upper and lower limbs, which implicates similar motor control mechanisms under the variety of locomotor constraints.

![Fig. 4](https://example.com/fig4.png)

Schematic illustration of the possible organization of neural mechanisms regulating rhythmic arm movement. CPG, central pattern generator; SMA, supplementary motor area; MLR, mesencephalic locomotor region; CBM, cerebellum. Adopted from Zehr et al.79.
reflex responses following stimulation of non-noxious cutaneous nerve were examined during human walking. These studies showed a phase-dependent modulation and reversal of reflex sign from suppressive to facilitative at the end of the swing phase in tibialis anterior muscle following tibial or sural nerve stimulation. It was argued that cutaneous reflexes play an important role in preserving balance during the step cycle.

1. Functional significance of the cutaneous reflexes during walking

To elucidate the functional linkage between reflex EMG responses and kinematic outcome, EMG recordings from the upper and lower leg muscles were measured and changes in joint kinematics were also recorded. In addition, the total net reflex effect of stimulation and net mechanical outcome were analyzed statistically. Reflexes to stimulation of these nerves were shown to have functional effects, particularly during swing or the swing to stance transition. SP nerve reflexes are functionally equivalent to the stumbling corrective response described by Forssberg in which the swing limb passes by the imposed obstacle to maintain a relatively unperturbed step cycle. As shown in Fig. 5, during early swing, SP nerve stimulation elicited a stumble corrective response involving ankle plantar flexion and knee flexion. Tibial nerve stimulation generated a withdrawal response at the stance to swing transition and a placing response at late swing. When stimulating the sural nerve during the swing phase, withdrawal of the foot from the stimulus point occurred. This was especially evident in TA and MG muscles from activation of the sural nerve because this caused a mechanical eversion and dorsiflexion of the ipsilateral foot. This response acts to stabilize the foot if there were pressure activation on the lateral foot border caused by uneven terrain in early stance. This response may assist in preventing an ankle sprain, which might result if excessive inversion occurred. These reflex outcomes during walking were quite different from outcomes investigated during standing, suggesting a contribution of CPG in humans.

Haridas et al. examined the amplitude of cutaneous reflexes of both the ipsilateral and contralateral legs electrically evoked from two nerves innervating different parts of the foot during walking with varying degrees of stability. They found that challenging the balance of the subjects during walking can lead to task-specific changes in reflex amplitudes, and that the influences are not related to a generalized change in reflex excitability; rather the changes observed are limited to specific reflex circuits at specific points in the step. Later, they showed that the strength of interlimb cutaneous reflexes was influenced by the level of postural threat. Thus, the excitability of cutaneous reflexes is thought to be flexibly tuned depending on the context of a behavior.

Modulation of interlimb reflex during rhythmic movement

1. Neurophysiological basis of the interlimb reflexes

In quadrupeds, there is a linkage between fore- and hind-limbs during locomotion. Specialized neural networks in the cervical and lumber spinal cord through propriospinal circuitry are thought to be responsible for the generation of rhythmic fore- and hind-limb locomotor activity in quadrupeds. Coupling of both neural networks may be mediated by the long ascending and descending propriospinal systems in the cervical and lumber spinal cord of the cat and rat. Juvin et al. reported the pharmacological nature of propriospinal interactions between cervical and lumbar locomotor CPGs in an isolated newborn rat spinal cord preparation. They showed independent rhythmogenic capabilities in the cervical and lumber locomotor regions, and an interconnection of both regions principally via propriospinal neural circuitry that extended from the rhythmogenic lumbar to cervical cord levels (see Fig. 6). They also demonstrated that both inhibitory and excitatory synaptic pathways from the lum-
bar generators coordinate cervical locomotor patterning, with ascending excitation playing a major role in lumbo-
cervical coupling. An interesting point may be dominance 
in locomotor drive from the lumbar generators over the 
cervical counterparts, i.e., caudorostral excitability gradi-
ent.

2. Interlimb reflexes in humans

Reflex studies in humans have shown that interlimb 
reflexes may play a crucial role in coordinating arm and 
leg movements during locomotion\(^6,8,9,90\). It was demonstr-
ated that there is natural frequency locking between 
upper and lower limb movement during walking, crawl-
ing and swimming\(^27\). These findings suggest that there 
are substantial similarities in coordination between upper 
and lower limbs in bipedal humans and that of fore- and 
hind-limbs in quadrupeds\(^6\). However, it remains unclear 
how tightly the upper and lower limbs are linked during 
rhythmic upper and lower limb movement in humans.

Zehr et al. showed that stimulation of cutaneous nerves 
inervating the hand (superficial radial, SR) and foot (su-
perficial peroneal, SP) elicits widespread reflex responses 
in many muscles across the body\(^21\). These interlimb re-
flex responses were suggested to be functionally relevant 
to assist in motor coordination between the arms and legs 
during motor tasks such as walking. The authors further 
tested the hypothesis to determine if interlimb reflexes 
were phase-dependently modulated and produced func-
tional kinematic changes during locomotion. They found 
that significant phase-dependent modulation (including 
reflex reversals) of interlimb cutaneous reflex responses 
was observed in remote limb muscles. The results suggest 
coordinated and functionally relevant reflex pathways 
from the SP and SR nerves onto motoneuron innervated 

![Fig. 6](image)

Fig. 6 Summary diagram of asymmetrical spinal pathways 
contributing to the coordination of the spatially distant 
rhythmicogenic networks underlying quadrupedal loco-
motion in the neonatal rat. E, Extensor; F, flexor. Ad-
opted from Juvin et al.\(^53\).

Recently, rhythmic movements other than walking were 
used as models for investigating the coordination between 
arm and leg movements in humans. Frigon et al.\(^70\) re-
ported that rhythmic arm cycling alters reflex excitability 
in stationary legs. In addition, Huang and Ferris\(^91\) dem-
strated that there was neural coupling between upper and 
lower limbs during recumbent stepping. They showed that 
rhythmic upper limb activity increased EMG amplitude 
in the lower limbs when subjects attempted to relax them. 
However, little is known about the interactions between 
upper and lower limbs when human subjects simultane-
ously perform rhythmic arm and leg movement.

If there is strong coupling of CPGs between the upper 
and lower limbs, cutaneous reflexes in the arm muscles 
can be influenced by rhythmic movement of the legs and 
vice versa. However, we have recently demonstrated that 
cutaneous reflexes in the arm muscles are little influenced 
by rhythmic movement of the legs, and vice versa, when 
subjects simultaneously performed AL cycling\(^92\). Based 
on these results, it was suggested that the reflex pathways 
responsible for the cutaneous reflexes in the arm (leg) are 
only weakly coupled with CPG in the leg (arm) during 
AL cycling. These results appear to contradict a recent 
perception that there is neuronal coupling of arm and leg 
movement during various human locomotor activities\(^6,8,27\). 
To further elucidate this discrepancy, we examined how 
coupling of both limbs is regulated during independent 
rhythmic movement of the arm and leg\(^93\). Subjects per-
formed simultaneous arm and leg cycling (AL cycling) 
at their preferred cadences without feedback for 10s, 
and then were asked to voluntarily change the cadence 
(increase, decrease, or stop) of arm or leg cycling. Leg 
cycling cadence was not affected by voluntary changes in 
arm cadence. By contrast, arm cycling cadence was sig-
ificantly altered when leg cycling cadence was changed. 
These results suggest the existence of a predominant 
lumbocervical rhythmic influence of leg cycling on 
arm movement during AL cycling. Taking these findings into 
consideration, the modulation of cutaneous reflexes dur-
ing AL cycling is most probably determined by CPGs that 
regulate the activity of a particular limb irrespective of 
whether the movement of other limbs is in-phase or 180 
degrees out of phase. The mutual interaction of CPGs be-
tween the upper and lower limbs may be weak during AL 
cycling; and rhythmically or simultaneously moving the 
arms and legs is insufficient for a tight coupling of CPGs 
between the arms and legs\(^6,92\).

In contrast, Balter et al.\(^76\) reported that rhythmic arm 
movement makes a significant phase-dependent contribu-
tion to cutaneous reflex expression in the legs during a 
combined arm and leg task. This effect is superimposed 
on the dominant effect of leg movement, suggesting that 
there exists coupling between the arms and legs in terms 
of functional relationships during similar rhythmic activi-
ties, such as walking. The authors further interpret this as evidence for commonalities in neural regulation among mammalian tetrapods, and that this is a predicted outcome for interactions between CPGs regulating arm and leg movement during human walking. One of the most important differences between the studies by Sakamoto et al. and Balter et al. is whether there was mechanical coupling between arm and leg ergometers. The former study was conducted with mechanically uncoupled arm and leg ergometers. In contrast, the latter study used mechanically coupled ones. This discrepancy may lead to subtle differences in strategy and motor outputs to perform arm and leg cycling. While performing arm and leg cycling with mechanically uncoupled ergometers, a higher motor center may differentially regulate arm and leg muscles to cope with biomechanical constraints specific to both ergometers. In addition, subjects may pay special attention to match the cadence of both arm and leg cycling. These factors would lead to differential regulation of CPGs through descending inputs from corticospinal and reticulospinal tracts and the cerebellum between AL cycling with coupled and uncoupled ergometers, which may explain the differential regulations of the excitability of the cutaneous reflexes.

One of difficulties to elucidating the functional coupling of neural circuits between the arm and leg involving rhythmic and locomotion in humans may be due to different strengths of oscillatory effect from CPGs to the arms and legs. When performing rhythmic arm and leg movement, the intralimb reflex effect is much stronger than the interlimb effect. Thus, during rhythmic arm and leg movement, significant changes in the reflex effect in given limb muscles can be easily masked by phase modulation coming from the intralimb effect. Recently, we examined to what extent the excitability of the early latency cutaneous reflexes (ELCR, peak latency ~30–70 ms) in the stationary arm muscles are modulated during different types of rhythmic leg cycling. The subjects performed leg pedaling (60 or 90 rpm) while simultaneously contracting their arm muscles isometrically. Control experiments included isolated isometric contractions and discrete movements of the leg. ELCRs were evoked by stimulation of the superficial radial nerve with a train of rectangular pulses (3 pulses at 333 Hz, intensity at 2.0- to 2.5-fold perceptual threshold). Reflex amplitudes were significantly increased in the flexor carpi radialis and posterior deltoid and significantly decreased in the biceps brachii muscles during leg pedaling compared with that
during stationary isometric contraction of the lower leg muscles (Fig. 8). This effect was also sensitive to cadence. However, no significant modulation was observed during the rhythmic isometric contractions or discrete one-shot-like cyclic movements of the leg. Additionally, there was no phase-dependent modulation of the ELCR. These findings suggest that activation of the rhythm generating system of the legs selectively affects the excitability of the early latency cutaneous reflex pathways in the arm muscles. In addition, these findings further support the contribution of an interlimb interaction between the presumed lower limb neural system and the neural circuit of the cutaneous reflex in the upper limbs. This would result in an increase of the excitability of the circuitry for the cutaneous reflex (offset regulation).
Conclusions

In this review, we discussed the unique gain regulation of cutaneous reflexes and H-reflex during locomotor movements in humans. Although there is some difference in reflex regulation between bipeds and quadrupeds, there are many functional similarities of reflex responses between them. Many previous studies suggested that the CPG system plays a key role in differential regulation of cutaneous reflex and H-reflex gain during locomotor movements and stationary contraction. However, the minimum requirement of cycling frequency, rotation and load for driving CPG in humans remains unclear. These factors should be elucidated in future studies to apply arm and leg cycling as rehabilitation training for patients with gait disorders. Also, the developmental aspects of reflex regulation during locomotor movement are little known, and need to be explored in the future.

References


